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PATENT APPLICATION

Title: ARYL ANILINE ß2 ADRENERGIC RECEPTOR AGONISTS

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Aryl Aniline β_2 Adrenergic Receptor Agonists

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/338,194, filed November 13, 2001 and U.S. Provisional Application No. 60/343,771, filed December 28, 2001, the entire disclosures of which are incorporated herein by reference.

Field of the Invention

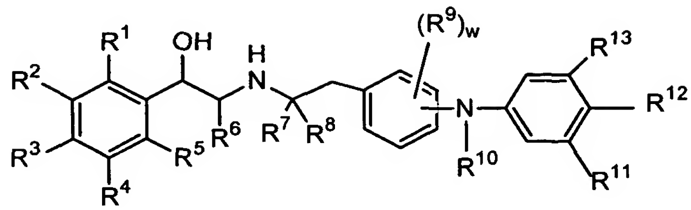
The invention is directed to novel β_2 adrenergic receptor agonists. The invention is also directed to pharmaceutical compositions comprising such compounds, methods of using such compounds to treat diseases associated with β_2 adrenergic receptor activity, and processes and intermediates useful for preparing such compounds.

Background of the Invention

β_2 adrenergic receptor agonists are recognized as effective drugs for the treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema). β_2 adrenergic receptor agonists are also useful for treating pre-term labor, and are potentially useful for treating neurological disorders and cardiac disorders. In spite of the success that has been achieved with certain β_2 adrenergic receptor agonists, current agents possess less than desirable potency, selectivity, speed of onset, and/or duration of action. Thus, there is a need for additional β_2 adrenergic receptor agonists having improved properties. Preferred agents may possess, among other properties, improved duration of action, potency, selectivity, and/or onset.

Summary of the Invention

The invention provides novel compounds that possess β_2 adrenergic receptor agonist activity. Accordingly, this invention provides compounds of formula (I):



(I)

wherein:

each of R^1-R^5 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, and R^a;

or R^1 and R^2, R^2 and R^3, R^3 and R^4, or R^4 and R^5 are joined together to form a group selected from the group consisting of $-C(R^d)=C(R^d)C(=O)NR^d-$, $-CR^dR^d-CR^dR^d-C(=O)NR^d-$, $-NR^dC(=O)C(R^d)=C(R^d)-$, $-NR^dC(=O)CR^dR^d-CR^dR^d-$, $-NR^dC(=O)S-$, $-SC(=O)NR^d-$, $-(CR^dR^d)_p-$, $-S(CR^dR^d)_q-$, $-(CR^dR^d)_qS-$, $-S(CR^dR^d)_rO-$, $-O(CR^dR^d)_rS-$, and $-NHC(R^j)=C(R^k)-$;

R^6 is hydrogen, alkyl, or alkoxy;

R^7 is hydrogen or alkyl;

R^8 is hydrogen or alkyl; or R^8 together with R^9 is $-CH_2-$ or $-CH_2CH_2-$;

R^9 is independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, and R^a, or R^9 together with R^8 is $-CH_2-$ or $-CH_2CH_2-$;

R^{10} is hydrogen or alkyl;

each R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-NO_2$, halo, $-NR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-OR^d$, $-S(O)_mR^d$, $-NR^d-NR^d-C(=O)R^d$, $-NR^d-N=CR^dR^d$, $-N(NR^dR^e)R^d$, and $-S(O)_2NR^dR^e$;

or R^{11} and R^{12} together with the atoms to which they are attached form a fused benzo ring, which benzo ring can optionally be substituted with 1, 2, 3, or 4 R^c;

or R^{11} and R^{12} together with the atoms to which they are attached form a heterocyclic ring;

wherein for R^1-R^6, R^9, and R^{11}-R^{13}, each alkyl, alkenyl, and alkynyl is optionally substituted with R^m, or with one or more (e.g. 1, 2, 3, or 4) substituents independently selected from R^b; for R^1-R^6, R^9, and R^{11}-R^{13}, each aryl and heteroaryl is optionally

substituted with 1, 2, 3, or 4 substituents independently selected from R^c, and for R^1-R^6, R^9, and R^{11}-R^{13} each cycloalkyl and heterocyclic ring is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^b and R^c;

each R^a is independently $-OR^d$, $-NO_2$, halo, $-S(O)_mR^d$, $-S(O)_2OR^d$, $-S(O)_mNR^dR^e$, $-NR^dR^e$, $-O(CR^fR^g)_nNR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-CO_2(CR^fR^g)_nCONR^dR^e$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-CR^d(=N-OR^e)$, $-CF_3$, or $-OCF_3$;

each R^b is independently R^a, oxo, or $=N-OR^e$;

each R^c is independently R^a, alkyl, alkenyl, or alkynyl; wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^b;

each R^d and R^e is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with one or more (e.g. 1, 2, 3, or 4) substituents independently selected from R^h; or R^d and R^e together with the atoms to which they are attached form a heterocyclic ring having from 5 to 7 ring atoms, wherein the heterocyclic ring optionally contains 1 or 2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen;

each R^f and R^g is independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl; wherein each alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^h; or R^f and R^g together with the carbon atom to which they are attached form a ring having from 5 to 7 ring atoms, wherein the ring optionally contains 1 or 2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

each R^h is independently halo, C_{1-8}alkyl, C_{1-8}alkoxy, $-S-C_{1-8}$alkyl, aryl, (aryl)-C_{1-6}alkyl, (aryl)-C_{1-8}alkoxy, heteroaryl, (heteroaryl)-C_{1-6}alkyl, (heteroaryl)-C_{1-8}alkoxy, hydroxy, amino, $-NHC_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, $-OC(=O)C_{1-6}$alkyl, $-C(=O)C_{1-6}$alkyl, $-C(=O)OC_{1-6}$alkyl, $-NHC(=O)C_{1-6}$alkyl, $-C(=O)NHC_{1-6}$alkyl, carboxy, nitro, -CN, or $-CF_3$;

R^j and R^k together with the carbon atoms to which they are attached form a phenyl ring that is optionally substituted with 1, 2, 3, or 4 R^c;

each R^m is independently aryl, heteroaryl, cycloalkyl or heterocyclyl; wherein each aryl or heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents selected from the

group consisting of R^c, and wherein each cycloalkyl and heterocyclyl is optionally substituted with 1, 2, 3, or 4 substituents selected from R^b;

m is 0, 1, or 2;

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is 3, 4, or 5;

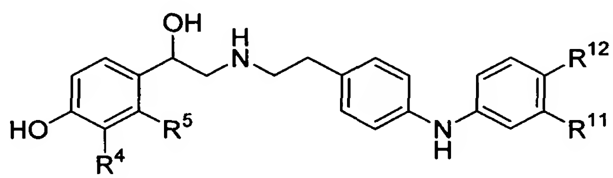
q is 2, 3, or 4;

r is 1, 2, or 3;

w is 0, 1, 2, 3, or 4;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

The invention also provides compounds of formula (II):



(II)

wherein:

R^4 is $-CH_2OH$ or -NHCHO and R^5 is hydrogen; or R^4 and R^5 taken together are -NHC(=O)CH=CH-;

R^{11} is phenyl or heteroaryl, wherein each phenyl is optionally substituted with 1 or 2 substituents selected from halo, $-OR^d$, -CN, $-NO_2$, $-SO_2R^d$, $-C(=O)R^d$, $-C(=O)NR^dR^e$, and C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with 1 or 2 substituents selected from carboxy, hydroxy, and amino, and each R^d and R^e is independently hydrogen or C_{1-3}alkyl; and wherein each heteroaryl is optionally substituted with 1 or 2 C_{1-3}alkyl substituents; and

R^{12} is hydrogen or $-OC_{1-6}$alkyl;

or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

The invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically-acceptable carrier.

The invention also provides a method of treating a disease or condition associated with β_2 adrenergic receptor activity (e.g. a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder,

or inflammation) in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound of the invention.

The invention also provides a method of treating a disease or condition associated with β_2 adrenergic receptor activity (e.g. a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder, or inflammation) in a mammal, comprising administering to the mammal, a therapeutically effective amount of a pharmaceutical composition of the invention.

This invention also provides a method of modulating a β_2 adrenergic receptor, the method comprising stimulating a β_2 adrenergic receptor with a modulatory amount of a compound of the invention.

In separate and distinct aspects, the invention also provides synthetic processes and novel intermediates, including compounds of formulas (III), (IV), and (VII) described herein, which are useful for preparing compounds of the invention.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating a disease or condition associated with β_2 adrenergic receptor activity (e.g. a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, a neurological disorder, a cardiac disorder, or inflammation) in a mammal.

Detailed Description of the Invention

When describing the compounds, compositions and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

The term "alkyl" refers to a monovalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Such alkyl groups preferably contain from 1 to 20 carbon atoms; more preferably, from 1 to 8 carbon atoms; and still more preferably, from 1 to 4 carbon atoms. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

The term "alkenyl" refers to a monovalent unsaturated hydrocarbon group containing at least one carbon-carbon double bond, typically 1 or 2 carbon-carbon double bonds, and which may be linear or branched or combinations thereof. Such alkenyl

groups preferably contain from 2 to 20 carbon atoms; more preferably from 2 to 8 carbon atoms; and still more preferably, from 2 to 4 carbon atoms. Representative alkenyl groups include, by way of example, vinyl, allyl, isopropenyl, but-2-enyl, *n*-pent-2-enyl, *n*-hex-2-enyl, *n*-hept-2-enyl, *n*-oct-2-enyl, *n*-non-2-enyl, *n*-dec-4-enyl, *n*-dec-2,4-dienyl and the like.

The term “alkynyl” refers to a monovalent unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, typically 1 carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Such alkynyl groups preferably contain from 2 to 20 carbon atoms; more preferably from 2 to 8 carbon atoms; and still more preferably, from 2 to 4 carbon atoms. Representative alkynyl groups include, by way of example, ethynyl, propargyl, but-2-ynyl and the like.

The term “alkoxy” refers to a group of the formula -OR, where R is an alkyl group as defined herein. Representative alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, *n*-pentoxy, *n*-hexoxy and the like.

The term “cycloalkyl” refers to a monovalent saturated carbocyclic group which may be monocyclic or multicyclic. Each ring of such cycloalkyl groups preferably contains from 3 to 10 carbon atoms. This term also includes cycloalkyl groups fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic (cycloalkyl) portion of the group. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,2,3,4-tetrahydronaphth-2-yl, decahydronaphthyl, indan-1-yl, adamantyl, norbornyl and the like.

The term “aryl” refers to a monovalent carbocyclic group which may be monocyclic or multicyclic (i.e., fused) wherein at least one ring is aromatic. Such aryl groups preferably contain from 6 to 20 carbon atoms; more preferably, from 6 to 10 carbon atoms. This term includes multicyclic carbocyclic ring systems wherein one or more rings are not aromatic, provided the point of attachment is on an aromatic ring. Representative aryl groups include, by way of example, phenyl, napthyl, azulenyl, indan-5-yl, 1,2,3,4-tetrahydronaphth-6-yl, and the like.

The term “heteroaryl” refers to a monovalent aromatic group that contains at least one heteroatom, preferably 1 to 4 heteroatoms, selected from N, S and O, and which may be monocyclic or multicyclic (i.e., fused). Such heteroaryl groups preferably contain from

5 to 20 atoms; more preferably, from 5 to 10 atoms. This term also includes heteroaryl groups fused to a cycloalkyl or aryl group, in which the point of attachment is on the aromatic (heteroaryl) portion of the group. Representative heteroaryl groups include, by way of example, pyrroyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl (or, equivalently, pyridinyl), oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, quinolyl, indolyl, isoquinolyl and the like.

The term "heterocyclyl" or "heterocyclic ring" refers to a saturated or partially unsaturated cyclic non-aromatic group, which may be monocyclic or multicyclic (i.e., fused or bridged), and which contains at least one heteroatom, preferably 1 to 4 heteroatoms, selected from N(X), S and O, wherein each X is independently hydrogen or alkyl. Such heterocyclyl groups preferably contain from 3 to 20 atoms; more preferably, from 3 to 10 atoms. This term also includes such a heterocyclyl group fused to one or more cycloalkyl, aryl, or heteroaryl groups. The point of attachment of the heterocyclyl group may be any carbon or nitrogen atom in a heterocyclyl, cycloalkyl, aryl or heteroaryl portion of the group. Representative heterocyclyl groups include, by way of example, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, morpholinyl, indolin-3-yl, 2-imidazolinyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, quinuclidinyl, 2-oxobenzopyran, and the like.

The term "halo" refers to a fluoro, chloro, bromo or iodo.

The term "oxo" refers to a group of the formula =O.

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a patient, such as a mammal (particularly a human), and includes:

(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient;

(c) suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

The phrase "disease or condition associated with β_2 adrenergic receptor activity" includes all disease states and/or conditions that are acknowledged now, or that are found in the future, to be associated with β_2 adrenergic receptor activity. Such disease states include, but are not limited to, bronchoconstrictive or pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema), as well as neurological disorders and cardiac disorders. β_2 Adrenergic receptor activity is also known to be associated with pre-term labor (see, for example, U.S. Patent No. 5,872,126) and some types of inflammation (see, for example, WO 99/30703 and U.S. Patent No. 5,290,815).

The term "pharmaceutically-acceptable salt" refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

Salts derived from pharmaceutically-acceptable acids include acetic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic, xinafoic (1-hydroxy-2-naphthoic acid) and the like. Particularly preferred are salts derived from fumaric, hydrobromic, hydrochloric, acetic, sulfuric, phosphoric, methanesulfonic, *p*-toluenesulfonic, xinafoic, tartaric, citric, malic, maleic, succinic, and benzoic acids.

Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Particularly preferred are ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occuring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine

resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, i.e. a compound of the invention or a pharmaceutically-acceptable salt thereof, and one or more molecules of a solvent. Such solvates are typically crystalline solids having a substantially fixed molar ratio of solute and solvent. Representative solvents include by way of example, water, methanol, ethanol, isopropanol, acetic acid, and the like. When the solvent is water, the solvate formed is a hydrate.

The term "leaving group" refers to a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

The term "amino-protecting group" refers to a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl; alkoxycarbonyl groups, such as *tert*-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS); and the like.

The term "hydroxy-protecting group" refers to a protecting group suitable for preventing undesired reactions at a hydroxy group. Representative hydroxy-protecting groups include, but are not limited to, alkyl groups, such as methyl, ethyl, and *tert*-butyl; acyl groups, for example alkanoyl groups, such as acetyl; arylmethyl groups, such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM); silyl groups, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS); and the like.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A specific value for R^1 is hydrogen.

A specific value for R^2 is hydrogen.

A specific value for R^3 is hydroxy.

A specific value for R^4 is $-CH_2OH$ or -NHCHO.

A specific value for R^5 is hydrogen.

A specific value for R^4 and R^5 together are -NHC(=O)CH=CH- or -SC(=O)NH-.

A specific value for R^6 is hydrogen.

A specific value for R^7 is hydrogen.

A specific value for R^8 is hydrogen.

A specific value for w is 0.

Another specific value for w is 1 or 2.

A specific value for R^9 together with R^8 is $-CH_2-$ or $-CH_2CH_2-$.

A specific value for R^{10} is hydrogen.

Another specific value for R^{10} is alkyl.

A specific value for R^{11} is hydrogen.

Another specific value for R^{11} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-NO_2$, halo, $-NR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-OR^d$, $-S(O)_mR^d$, $-NR^d-NR^d-C(=O)R^d$, $-NR^d-N=CR^dR^d$, $-N(NR^dR^e)R^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{11} is hydrogen, alkyl, heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{11} is heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{11} is $-OR^d$.

Another specific value for R^{11} is $-S(O)_mR^d$.

A specific value for R^{12} is hydrogen.

Another specific value for R^{12} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-NO_2$, halo, $-NR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-OR^d$, $-S(O)_mR^d$, $-NR^d-NR^d-C(=O)R^d$, $-NR^d-N=CR^dR^d$, $-N(NR^dR^e)R^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{12} is hydrogen, alkyl, heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

A specific value for R^{12} is heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{12} is $-OR^d$.

Another specific value for R^{12} is $-S(O)_mR^d$.

Another specific value for R^{12} is $-S(O)_2NR^dR^e$.

A specific value for R^{13} is hydrogen.

Another specific value for R^{13} is alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-NO_2$, halo, $-NR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-OR^d$, $-S(O)_mR^d$, $-NR^d$-NR^d-$C(=O)R^d$, $-NR^d$-$N=CR^dR^d$, $-N(NR^dR^e)R^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{13} is hydrogen, alkyl, heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

Another specific value for R^{13} is heterocyclyl, $-OR^d$, $-S(O)_mR^d$, or $-S(O)_2NR^dR^e$.

A specific value for R^{13} is $-OR^d$.

A specific value for R^{13} is $-S(O)_mR^d$.

A specific group of compounds of the invention are compounds wherein each of R^1-R^4 is independently selected from the group consisting of hydrogen, fluoro, chloro, amino, hydroxy, *N,N*-dimethylaminocarbonyloxy, $-CH_2OH$, and -NHCHO, and R^5 is hydrogen; or R^1 is hydrogen, R^2 is hydrogen, R^3 is hydroxy, and R^4 and R^5 together are -NHC(=O)CH=CH- or -SC(=O)NH-.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is chloro; R^3 is amino; R^4 is chloro; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is *N,N*-dimethylaminocarbonyloxy; R^3 is hydrogen; R^4 is *N,N*-dimethylaminocarbonyloxy; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen, fluoro, or chloro; R^2 is hydroxy; R^3 is hydrogen; R^4 is hydroxy; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is chloro; R^2 is hydrogen; R^3 is hydroxy; R^4 is hydrogen; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is hydrogen; R^3 is hydroxy; R^4 is $-CH_2OH$; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is hydrogen; R^3 is hydroxy; R^4 is -NHCHO; and R^5 is hydrogen.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is hydrogen; R^3 is hydroxy; and R^4 and R^5 together are -NHC(=O)CH=CH-.

A specific group of compounds of the invention are compounds wherein R^1 is hydrogen; R^2 is hydrogen; R^3 is hydroxy; and R^4 and R^5 together are -SC(=O)NH-.

A specific group of compounds of the invention are compounds wherein R^{11} is hydrogen, R^{12} is $-SR^d$; R^{13} is hydrogen; and R^d is alkyl, aryl, or heteroaryl.

A specific group of compounds of the invention are compounds wherein R^{11} is $-SR^d$, R^{12} is hydrogen; R^{13} is hydrogen; and R^d is alkyl, aryl, heteroaryl.

When part of the group $-SR^d$, a specific value for R^d is alkyl.

When part of the group $-SR^d$, another specific value for R^d is C_{1-6}alkyl.

When part of the group $-SR^d$, another specific value for R^d is C_{1-3}alkyl.

When part of the group $-SR^d$, another more specific value for R^d is aryl optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, $-N(C_{1-6}alkyl)_2$, nitro, -CN, and $-CF_3$.

When part of the group $-SR^d$, another more specific value for R^d is phenyl optionally substituted with 1, 2, 3, or 4 substituents independently selected from fluoro and C_{1-3}alkyl.

A specific group of compounds of the invention are compounds wherein R^{11} or R^{12} is methylthio, 2-methylphenylthio, 4-methyl-2-pyrimidylthio, 4-fluorophenylthio, or 4-methylphenylthio.

A specific group of compounds of the invention are compounds wherein R^{11} is hydrogen or alkyl, R^{12} is $-SO_2NR^dR^e$; and R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} is $-SO_2NR^dR^e$, R^{12} is hydrogen or alkyl; and R^{13} is hydrogen.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d is alkyl, aryl, or heteroaryl; and for R^e is hydrogen, alkyl, aryl, or heteroaryl; wherein each alkyl, aryl, or heteroaryl, is optionally substituted with one or more (e.g. 1, 2, 3, or 4) substituents independently selected from R^h; or R^d and R^e together with the nitrogen atom to which they are attached is a heterocyclic ring having from 5 to 7 ring atoms, wherein the heterocyclic ring optionally contains 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d and R^e independently is hydrogen, alkyl, aryl, or heteroaryl; wherein each alkyl, aryl, or heteroaryl, is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^h.

As a substituent as part of the group $-SO_2NR^dR^e$, a specific value for R^h is halo, C_{1-8}alkyl, C_{1-8}alkoxy, -S-C_{1-8}alkyl, aryl, hydroxy, amino, -NHC_{1-6}alkyl, -N(C_{1-6}alkyl)$_2$, -OC(=O)C_{1-6}alkyl, -C(=O)C_{1-6}alkyl, -C(=O)OC_{1-6}alkyl, -NHC(=O)C_{1-6}alkyl, -C(=O)NHC_{1-6}alkyl, carboxy, nitro, -CN, or $-CF_3$.

Another specific value for R^h in the above context is halo, C_{1-6}alkyl, C_{1-6}alkoxy, or $-CF_3$.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d and R^e together with the nitrogen atom to which they are attached is a heterocyclic ring having from 5 to 7 ring atoms, wherein the heterocyclic ring optionally contains 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d and R^e independently is alkyl; wherein each alkyl is optionally substituted with 1 or 2 alkoxy substituents.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d or R^e is phenyl, or naphthyl; wherein each phenyl and naphthyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, and $-CF_3$.

When part of the group $-SO_2NR^dR^e$, a specific value for R^d or R^e is heteroaryl; wherein each heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, and $-CF_3$. Preferably heteroaryl is pyridyl, pyrimidyl, or thiazolyl.

A preferred group of compounds are compounds wherein R^{11} or R^{12} is $-SO_2NR^dR^e$; wherein R^d is 4-heptyl-6-methyl-2-pyrimidyl, 5-methoxy-2-pyrimidyl, 2-pyridyl, phenyl, 2,6-dimethylphenyl, 2-thiazoyl, 2-trifluoromethylphenyl, or 3,5-dichlorophenyl; and R^e is hydrogen or ethyl.

Another preferred group of compounds are compounds of the invention wherein R^{11} or R^{12} is $-SO_2NR^dR^e$; wherein R^d and R^e together with the atoms to which they are attached are piperidino or morpholino.

A specific group of compounds of the invention are compounds wherein R^{11} is hydrogen or alkyl; R^{12} is $-SO_2R^d$; and R^{13} is hydrogen.

Another specific group of compounds of the invention are compounds wherein R^{11} is $-SO_2R^d$; R^{12} is hydrogen or alkyl; and R^{13} is hydrogen.

When part of the group $-SO_2R^d$, a specific value for R^d is alkyl, aryl, or heteroaryl.

When part of the group $-SO_2R^d$, a specific value for R^d is aryl optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, and $-CF_3$.

When part of the group $-SO_2R^d$, a specific value for R^d is phenyl optionally substituted with 1 or 2 substituents independently selected from halo and C_{1-6}alkyl.

A preferred group of compounds of the invention are compounds wherein R^{11} or R^{12} is $-SO_2R^d$; wherein R^d is phenyl, 4-chlorophenyl, methyl, or 4-fluorophenyl.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is $-OR^d$ and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo; wherein any alkyl or -O-alkyl is optionally substituted with aryl, or with one or more (e.g. 1, 2, 3, or 4) halo substituents.

A specific group of compounds of the invention are compounds wherein R^{11} is $-OR^d$.

A specific group of compounds of the invention are compounds wherein R^{12} is $-OR^d$

A specific group of compounds of the invention are compounds wherein R^{13} is $-OR^d$

A specific group of compounds of the invention are compounds wherein R^{11} is hydrogen; R^{12} is $-OR^d$; and R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} is $-OR^d$; R^{12} is hydrogen; and R^{13} is hydrogen.

When part of the group $-OR^d$, a specific value for R^d is alkyl, optionally substituted with one or more (e.g. 1, 2, 3, or 4) halo substituents and also optionally substituted with 1, 2, 3, or 4 aryl substituents, wherein each aryl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, $-NHC_{1-6}$alkyl, $-N(C_{1-6}alkyl)_2$, $-OC(=O)C_{1-6}$alkyl, $-C(=O)C_{1-6}$alkyl, $-C(=O)OC_{1-6}$alkyl, $-NHC(=O)C_{1-6}$alkyl, $-C(=O)NHC_{1-6}$alkyl, carboxy, nitro, -CN, and $-CF_3$.

When part of the group $-OR^d$, a specific value for R^d is alkyl, optionally substituted with one or more (e.g. 1, 2, 3, or 4) halo substituents and also optionally substituted with 1 or 2 phenyl substituents, wherein each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, -CN, and $-CF_3$.

A specific group of compounds of the invention are compounds wherein R^{11} and R^{12} together with the atoms to which they are attached form a saturated or unsaturated 5, 6, or 7 membered ring comprising one or more carbon atoms and 1 or 2 heteroatoms independently selected from oxygen, sulfur or nitrogen; and R^{13} is selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo; wherein any alkyl or -O-alkyl is optionally substituted with aryl, or with one or more (e.g. 1, 2, 3, or 4) halo substituents.

A more specific group of compounds of the invention are compounds wherein R^{11} and R^{12} together are $-OCH_2O-$, $-OCH_2CH_2O-$, or $-OCH_2CH_2\,CH_2O-$.

A specific group of compounds of the invention are compounds wherein R^{11}, R^{12}, or R^{13} is methoxy, ethoxy, benzyloxy, or isopropoxy.

A specific group of compounds of the invention are compounds wherein R^{11}, R^{12}, and R^{13} are each hydrogen.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is alkyl and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, hydroxy, and halo, wherein any alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents; or wherein R^{11} and R^{12} together with the atoms to which they are attached form a saturated or unsaturated 5, 6, or 7 membered carbocyclic ring.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is alkyl and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, hydroxy, and halo, wherein any alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents.

A specific group of compounds of the invention are compounds wherein R^{11} and R^{12} together with the atoms to which they are attached form a saturated or unsaturated 5, 6, or 7 membered carbocyclic ring; and R^{13} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, hydroxy, and halo, wherein any alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents.

A specific value for R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} is hydrogen; R^{12} is alkyl; and R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} is alkyl; R^{12} is hydrogen; and R^{13} is hydrogen.

A preferred group of compounds of the invention are compounds wherein R^{11} or R^{12} is methyl, ethyl, isopropyl, or cyclohexyl; or wherein R^{11} and R^{12} taken together are $-CH_2CH_2CH_2-$.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is aryl; and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo, wherein any alkyl or -O-alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents;

or wherein R^{11} and R^{12} together with the atoms to which they are attached form a fused benzo ring, which benzo ring can optionally be substituted with 1, 2, 3, or 4 R^c; and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo, wherein any alkyl or -O-alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is aryl; and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo, wherein any alkyl or -O-alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents.

A specific group of compounds of the invention are compounds wherein R^{11} is phenyl, optionally substituted with 1, 2, 3, or 4 alkyl, $-OR^d$, $-NO_2$, halo, $-NR^dR^e$, $-C(=O)R^d$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OC(=O)NR^dR^e$, $-NR^dC(=O)OR^e$, $-NR^dC(=O)NR^dR^e$, $-CR^d(=N-OR^e)$, $-CF_3$, or $-OCF_3$; R^{12} is selected from the group consisting of hydrogen and -O-alkyl, optionally substituted with aryl, or with one or more (e.g. 1, 2, 3, or 4) halo; and R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} is phenyl, optionally substituted with 1, 2, 3, or 4 alkyl, $-OR^d$, halo, $-CF_3$, or $-OCF_3$; R^{12} is selected from the group consisting of hydrogen and -O-alkyl, optionally substituted with aryl, or with one or more (e.g. 1, 2, 3, or 4) halo; and R^{13} is hydrogen.

A specific group of compounds of the invention are compounds wherein R^{11} or R^{12} is phenyl.

A specific group of compounds of the invention are compounds wherein R^{11} and R^{12} together with the atoms to which they are attached form a fused benzo ring.

A specific group of compounds of the invention are compounds wherein at least one of R^{11}, R^{12}, and R^{13} is heterocyclyl; and each of the other two of R^{11}, R^{12}, and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo, wherein any alkyl or -O-alkyl is optionally substituted with aryl, with one or more (e.g. 1, 2, 3, or 4) halo, or with 1 or 2 -O-alkyl substituents;

or wherein R^{11} and R^{12} together with the atoms to which they are attached form a heterocyclic ring.

A specific group of compounds of the invention are compounds wherein R^{11} and R^{12} together with the atoms to which they are attached form a saturated or unsaturated 5, 6, or 7 membered ring comprising carbon atoms and optionally comprising 1 or 2 heteroatoms independently selected from oxygen, sulfur or nitrogen, wherein said ring can optionally be substituted on carbon with one or two oxo (=O), and wherein said ring is fused to a benzo ring, which benzo ring can optionally be substituted with 1, 2, 3, or 4 R^c; and R^{13} is independently selected from the group consisting of hydrogen, alkyl, -O-alkyl, and halo, wherein any alkyl or -O-alkyl is optionally substituted with aryl, with one or more halo, or with 1 or 2 -O-alkyl substituents.

A specific group of compounds of the invention are compounds wherein R^{11} or R^{12} is 2,3-dihydro-5-methyl-3-oxo-1-pyrazolyl; or wherein R^{11} and R^{12} together with the atoms to which they are attached form a 2-oxobenzopyran ring.

Another specific group of compounds of the invention are compounds wherein R^{11} or R^{12} is anilino, trifluoromethoxy, or methoxycarbonyl.

A sub-group of compounds of the invention are compounds of formula (I) wherein each of R^1-R^5 is independently selected from the group consisting of hydrogen, alkyl, and R^a; wherein each R^a is independently $-OR^d$, halo, $-NR^dR^e$, $-NR^dC(=O)R^e$, or $-OC(=O)NR^dR^e$;

or R^1 and R^2, or R^4 and R^5, are joined together to form a group selected from the group consisting of $-C(R^d)=C(R^d)C(=O)NR^d-$, $-CR^dR^d-CR^dR^d-C(=O)NR^d-$, $-NR^dC(=O)C(R^d)=C(R^d)-$, $-NR^dC(=O)CR^dR^d-CR^dR^d-$, $-NR^dC(=O)S-$, and $-SC(=O)NR^d-$;

R^6, R^8, and R^{10} are each hydrogen;

each of $R^{11}$and R^{12} is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-NO_2$, halo,

$-NR^dR^e$, $-CO_2R^d$, $-OC(=O)R^d$, -CN, $-C(=O)NR^dR^e$, $-NR^dC(=O)R^e$, $-OR^d$, $-S(O)_mR^d$, $-NR^d-NR^d-C(=O)R^d$, $-NR^d-N=CR^dR^d$, $-N(NR^dR^e)R^d$, and $-S(O)_2NR^dR^e$;

wherein for R^1-R^5, R^{11}, and R^{12}, each alkyl is optionally substituted with R^m, or with 1, 2, 3, or 4 substituents independently selected from R^b; for R^{11} and R^{12}, each aryl and heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^c, and for R^{11} and R^{12}, each cycloalkyl and heterocyclyl is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^b and R^c;

R^{13} is hydrogen;

the group comprising $-NR^{10}$ is meta or para to the group comprising R^7; and

w is 0, 1, or 2.

Preferably within the above sub-group of compounds, each of R^{11} and R^{12} is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl, $-OR^d$, $-S(O)_mR^d$, and $-S(O)_2NR^dR^e$; wherein each alkyl is optionally substituted with 1 or 2 substituents independently selected from R^b, each aryl is optionally substituted with 1 or 2 substituents independently selected from R^c, and each heterocyclyl is optionally substituted with 1 or 2 substituents independently selected from R^b and R^c; and m is 0 or 2.

More preferably for such compounds, R^7 is hydrogen;

each of R^{11} and R^{12} is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, cyclohexyl, phenyl, pyrazolinyl, $-OR^d$, $-S(O)_mR^d$, and $-S(O)_2NR^dR^e$;

w is 0; and

R^d and R^e are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl, $-CF_3$, and C_{1-3}alkyl, pyridyl, thiazolyl, pyrimidinyl, and pyrazolinyl, where each phenyl is optionally substituted with 1 or 2 substitutents independently selected from halo, $-CF_3$, and C_{1-3}alkyl, each pyrimidinyl is optionally substituted with 1 or 2 substitutents independently selected from C_{1-3}alkyl and OC_{1-3}alkyl, and each pyrazolinyl is optionally substituted with 1 or 2 substitutents independently selected from C_{1-3}alkyl and carboxy; or

R^d and R^e, together with the nitrogen atom to which they are attached are morpholino or piperidino.

Within the more preferred sub-group, one most preferred sub-group of compounds are compounds wherein R^{11} is $-SR^d$ and R^{12} is hydrogen, or R^{11} is hydrogen and R^{12} is $-SR^d$, wherein R^d is selected from the group consisting of C_{1-3}alkyl, phenyl, and

pyrimidinyl, and wherein each phenyl is optionally substituted with 1 or 2 substitutents independently selected from halo and C_{1-3} alkyl, and each pyrimidinyl is optionally substituted with C_{1-3}alkyl.

Another most preferred sub-group of compounds are compounds wherein R^{11} is $-S(O)_2NR^dR^e$ and R^{12} is hydrogen or alkyl, or R^{11} is hydrogen or alkyl and R^{12} is $-S(O)_2NR^dR^e$, wherein R^d and R^e are independently selected from the group consisting of hydrogen, C_{1-3}alkyl, phenyl, pyridyl, thiazolyl, and pyrimidinyl, and wherein each phenyl is optionally substituted with 1 substitutent selected from halo and C_{1-3} alkyl, and each pyrimidinyl is optionally substituted with 1 substitutent selected from C_{1-3} alkyl and O-C_{1-3} alkyl; or R^d and R^e, together with the nitrogen atom to which they are attached are morpholino or piperidino.

Another most preferred sub-group of compounds are compounds wherein R^{11} is $-SO_2R^d$ and R^{12} is hydrogen, or R^{11} is hydrogen and R^{12} is $-SO_2R^d$, wherein R^d is C_{1-3}alkyl or phenyl, and wherein each phenyl is optionally substituted with 1 substituent selected from halo and C_{1-3}alkyl.

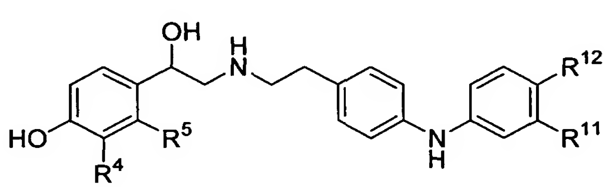
Another most preferred sub-group of compounds are compounds wherein R^{11} is $-OR^d$ and R^{12} is hydrogen or $-OR^d$; or R^{11} is hydrogen and R^{12} is $-OR^d$, wherein R^d is C_{1-3}alkyl.

Another most preferred sub-group of compounds are compounds wherein R^{11} is C_{1-3}alkyl and R^{12} is hydrogen or C_{1-3}alkyl; or R^{11} is cyclohexane and R^{12} is hydroxy.

Another most preferred sub-group of compounds are compounds wherein R^{11} is hydrogen or phenyl; and R^{12} is $-OC_{1-3}$alkyl; or wherein R^{11} is phenyl and R^{12} is hydrogen.

Yet another most preferred sub-group of compounds within the more preferred sub-group defined above are compounds wherein R^{12} is hydrogen and R^{11} is $SO_2NR^dR^e$, wherein R^d and R^e, together with the nitrogen atom to which they are attached, are morpholino or piperidino.

Another preferred group of compounds of formula (I) are compounds of formula (II):



(II)

wherein:

R^4 is $-CH_2OH$ or -NHCHO and R^5 is hydrogen; or R^4 and R^5 taken together are -NHC(=O)CH=CH-;

R^{11} is phenyl or heteroaryl, wherein each phenyl is optionally substituted with 1 or 2 substituents selected from halo, $-OR^d$, -CN, $-NO_2$, $-SO_2R^d$, $-C(=O)R^d$, $-C(=O)NR^dR^e$, and C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with 1 or 2 substituents selected from carboxy, hydroxy, and amino, and each R^d and R^e is independently hydrogen or C_{1-3}alkyl; and wherein each heteroaryl is optionally substituted with 1 or 2 C_{1-3}alkyl substituents; and

R^{12} is hydrogen or $-OC_{1-6}$alkyl.

More preferably, for compounds of formula (II), R^{11} is phenyl, optionally substituted with 1 or 2 substituents selected from halo, $-OR^d$, -CN, $-NO_2$, $-SO_2R^d$, $-C(=O)R^d$, and C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with 1 or 2 substituents selected from carboxy, hydroxy, and amino, and R^d is hydrogen or C_{1-3}alkyl; or R^{11} is pyridyl, thiophenyl, furanyl, pyrrolyl, isoxazolyl, or indolyl, each of which is optionally substituted with 1 or 2 C_{1-3}alkyl substituents.

Most preferable are compounds of formula (II), wherein R^{11} is phenyl, pyridyl, or thiophenyl, wherein each phenyl is optionally substituted with 1 substituent selected from the group consisting of chloro, $-OCH_3$, -CN, and $-CH_2NH_2$; and R^{12} is hydrogen, $-OCH_3$, or $-OC_2H_5$. Among most preferred compounds, particularly preferred are compounds of formula (II) wherein R^4 and R^5 taken together are -NHC(=O)CH=CH-, R^{11} is phenyl or pyridyl, wherein each phenyl is optionally substituted with 1 substituent selected from the group consisting of chloro, $-OCH_3$, -CN, and $-CH_2NH_2$, and R^{12} is $-OCH_3$.

A preferred compound is any one of compounds **1-102** shown in the Examples below.

Most preferred compounds of the invention include the following:

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine; and

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine;

N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(2-chlorophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(2-methoxyphenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(3-cyanophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(4-aminomethylphenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(3-chlorophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(4-aminomethylphenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(3-cyanophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(4-hydroxyphenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(3-pyridyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(3-pyridyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(4-pyridyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine;

N-{2-[4-(3-(thiophen-3-yl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine; and

N-{2-[4-(3-(3-chlorophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine.

The compounds of the invention contain one or more chiral centers Accordingly, the invention includes racemic mixtures, pure stereoisomers (i.e. individual enantiomers or diastereomers), and stereoisomer-enriched mixtures of such isomers, unless otherwise indicated. When a particular stereoisomer is shown, it will be understood by those skilled in the art, that minor amounts of other stereoisomers may be present in the compositions of this invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. In particular, compounds of the invention contain a chiral center at the alkylene carbon in formulas (I) and (II) to which the hydroxy group is attached. When a mixture of stereoisomers is employed, it is advantageous for the amount of the stereoisomer with the (*R*) orientation at the chiral center bearing the hydroxy group to be greater than the amount of the corresponding (*S*) stereoisomer. When comparing stereoisomers of the same compound, the (*R*) stereoisomer is preferred over the (*S*) stereoisomer.

<u>General Synthetic Procedures</u>

The compounds of the invention can be prepared using the methods and procedures described herein, or using similar methods and procedures. It will be

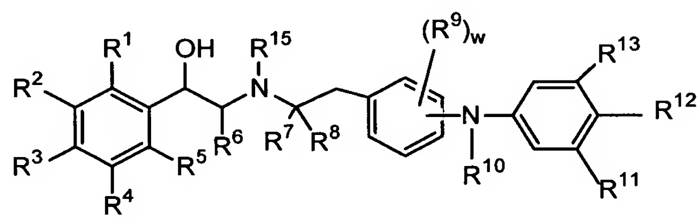
appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be used to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group, as well as suitable conditions for protection and deprotection, are well known in the art. Representative examples of amino-protecting groups and hydroxy-protecting groups are given above. Typical procedures for their removal include the following. An acyl amino-protecting group or hydroxy-protecting group may conveniently be removed, for example, by treatment with an acid, such as trifluoroacetic acid. An arylmethyl group may conveniently be removed by hydrogenolysis over a suitable metal catalyst such as palladium on carbon. A silyl hydroxy-protecting group may conveniently be removed by treatment with a fluoride ion source, such as tetrabutylammonium fluoride, or by treatment with an acid, such as hydrochloric acid.

In addition, numerous protecting groups (including amino-protecting groups and hydroxy-protecting groups), and their introduction and removal, are described in Greene and Wuts, *Protecting Groups in Organic Synthesis*, 2nd Edition, John Wiley & Sons, NY, 1991, and in McOmie, *Protecting Groups in Organic Chemistry*, Plenum Press, NY, 1973.

Processes for preparing compounds of the invention are provided as further embodiments of the invention and are illustrated by the procedures below.

A compound of formula (I) can be prepared by deprotecting a corresponding compound of formula (III):



(III)

wherein R^{15} is an amino-protecting group. Accordingly, the invention provides a method for preparing a compound of formula (I), comprising deprotecting a corresponding

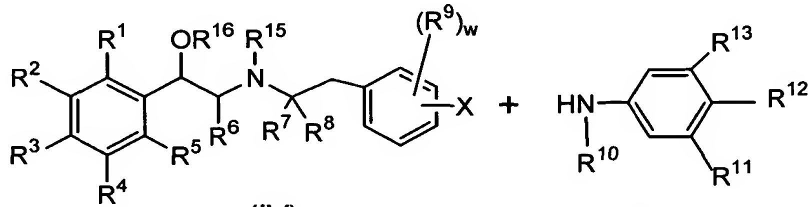
compound of formula (III), wherein R^{15} is an amino-protecting group (e.g. 1,1-(4-methoxyphenyl)methyl or benzyl).

A compound of formula (I) wherein R^3 is hydroxy can be prepared by deprotecting a corresponding compound of formula (I) wherein R^3 is $-OPg^1$ and Pg^1 is a hydroxy-protecting group. Accordingly, the invention provides a method for preparing a compound of formula (I) wherein R^3 is hydroxy, comprising deprotecting a corresponding compound of formula (I) wherein R^3 is $-OPg^1$ and Pg^1 is a hydroxy-protecting group (e.g. benzyl).

A compound of formula (I) wherein R^3 is hydroxy can also be prepared by deprotecting a corresponding compound of formula (III) wherein R^{15} is an amino-protecting group and wherein R^3 is $-OPg^1$ wherein Pg^1 is a hydroxy-protecting group. Accordingly, the invention provides a method for preparing a compound of formula (I), comprising deprotecting a corresponding compound of formula (III) wherein R^{15} is an amino-protecting group (e.g. benzyl) and R^3 is $-OPg^1$ wherein Pg^1 is a hydroxy-protecting group (e.g. benzyl).

The invention also provides an intermediate compound of formula (III) wherein R^{15} is an amino-protecting group (e.g. 1,1-di-(4'-methoxyphenyl)methyl or benzyl); as well as an intermediate compound of formula (I) wherein R^3 is $-OPg^1$ and Pg^1 is a hydroxy-protecting group; and an intermediate compound of formula (III) wherein R^{15} is an amino-protecting group (e.g. benzyl), R^3 is $-OPg^1$, and Pg^1 is a hydroxy-protecting group (e.g. benzyl).

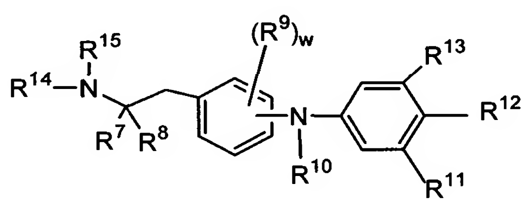
An intermediate compound of formula (III) can be prepared by reacting an amine of formula (V) with a compound of formula (IV), wherein R^{16} is hydrogen or a hydroxy-protecting group (e.g. *tert*-butyldimethylsilyl) and X is a suitable leaving group (e.g. bromo).



(IV) (V)

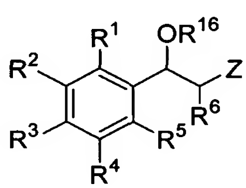
Accordingly, the invention provides a method for preparing a compound of formula (III), comprising reacting a corresponding aniline of formula (V) with a corresponding compound of formula (IV), wherein X is a suitable leaving group (e.g. bromo) and R^{15} is an amino-protecting group, in the presence of a transition metal catalyst. When R^{16} is a hydroxy-protecting group, the intermediate formed by the reaction of a compound of formula (V) with a compound of formula (IV) is subsequently deprotected to form the intermediate of formula (III). Suitable conditions for this reaction as well as suitable leaving groups are illustrated in the Examples and are also known in the art.

A compound of formula (III) can also be prepared by reacting an amine of formula (VII):

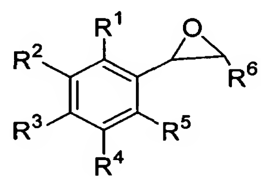


(VII)

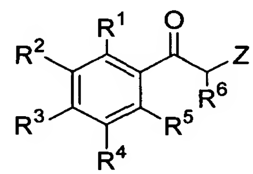
wherein R^{14} is hydrogen and R^{15} is an amino-protecting group (e.g. benzyl), with a compound of formula (VI), (VIII), or (IX):



(VI)



(VIII)



(IX)

wherein R^{16} is hydrogen or a hydroxy-protecting group (e.g. *tert*-butyldimethylsilyl) and Z is a leaving group.

Accordingly, the invention provides a method for preparing a compound of formula (III), comprising reacting a corresponding amine of formula (VII), wherein R^{14} is hydrogen and R^{15} is an amino-protecting group, with a corresponding compound of formula (VI), (VIII), or (IX), wherein R^{16} is hydrogen or a hydroxy-protecting group and Z is a suitable leaving group (e.g. bromo). When R^{16} is a hydroxy-protecting group, the intermediate formed by the reaction of a compound of formula (VII) with a compound of formula (VI) is subsequently deprotected to form the intermediate of formula (III).

The invention also provides a method for preparing a compound of formula (I), wherein R^3 is -OPg^1 and Pg^1 is a hydroxy-protecting group, comprising reacting a corresponding compound of formula (VII) wherein R^{14} and R^{15} are each hydrogen with a corresponding compound of formula (VI), wherein R^3 is -OPg^1 and Pg^1 is a hydroxy-protecting group and R^{16} is a hydroxy-protecting group.

Depending on the specific values of the substituents, variations on the synthetic schemes described above can be employed, particularly in the order of coupling and deprotection reactions, to produce a compound of the invention. For example, a compound of formula (I) wherein R^3 is hydroxy and R^{12} and R^{13} are hydrogen can be prepared by reacting an intermediate of formula (I) wherein R^3 is -OPg^1, where Pg^1 is a hydroxy-protecting group, and R^{11} is a suitable leaving group (e.g. bromo) with an appropriately substituted boronic acid to form an intermediate, which is subsequently deprotected, as illustrated in Examples 65-102.

Additionally, a useful intermediate for preparing a compound of formula (VII), wherein R^{14} is hydrogen and R^{15} is an amino-protecting group, is a corresponding compound of formula (VII) wherein R^{14} is an amino-protecting group that can be removed in the presence of R^{15}. A compound of formula (VII) wherein R^{14} is hydrogen and R^{15} is an amino-protecting group is itself also a useful intermediate for the preparation of a compound of formula (VII) where both R^{14} and R^{15} are hydrogen. Thus, the invention also provides novel intermediates of formula (VII), wherein R^{14} is hydrogen or an amino-protecting group, R^{15} is hydrogen or an amino-protecting group, and wherein R^7-R^{13} and w have any of the values defined herein, or a salt thereof.

A preferred compound of formula (VII) is a compound wherein R^{14} and R^{15} are both hydrogen. Another preferred compound of formula (VII) is a compound wherein R^{14} is an alkoxycarbonyl protecting group (e.g. *tert*-butoxy carbonyl), and R^{15} is an arylmethyl protecting group (e.g. benzyl). Another preferred compound of formula (VII) is a compound wherein R^{14} is hydrogen, and R^{15} is an alkoxycarbonyl protecting group (e.g. *tert*-butoxy carbonyl).

Pharmaceutical Compositions

The invention also provides pharmaceutical compositions comprising a compound of the invention. Accordingly, the compound, preferably in the form of a pharmaceutically-acceptable salt, can be formulated for any suitable form of administration, such as oral or parenteral administration, or administration by inhalation.

By way of illustration, the compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of powders, tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions will contain from about 0.05 to about 90% by weight of the active compound, and more generally from about 0.1 to about 30%. The pharmaceutical compositions may contain common carriers and excipients, such as cornstarch or gelatin, lactose, magnesium sulfate, magnesium stearate, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, cornstarch, sodium starch glycolate and alginic acid.

A liquid composition will generally consist of a suspension or solution of the compound or pharmaceutically-acceptable salt in a suitable liquid carrier(s), for example ethanol, glycerine, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, optionally with a suspending agent, a solubilizing agent (such as a cyclodextrin), preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder.

For example a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose and binders, for example polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example by incorporation of active compound and

excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of active compound and high molecular weight polyethylene glycol can be prepared and filled into a hard gelatin capsule; or a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil can be prepared and filled into a soft gelatin capsule.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, poly-vinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. Additionally, it may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

The compounds of the invention and their pharmaceutically-acceptable salts that are active when given parenterally can be formulated for intramuscular, intrathecal, or intravenous administration.

A typical composition for intra-muscular or intrathecal administration will consist of a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous or intrathecal administration will consist of a sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride, or a mixture of dextrose and sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus dextrose injection, Normosol-M and dextrose, Isolyte E, acylated Ringer's injection, and the like. Optionally, a co-solvent, for example, polyethylene glycol; a chelating agent, for example, ethylenediamine tetracetic acid; a solubilizing agent, for example, a cyclodextrin; and an anti-oxidant, for example, sodium metabisulphite, may be included in the formulation. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

The compounds of this invention and their pharmaceutically-acceptable salts which are active on topical administration can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous or discontinuous infusion of

the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, for example, U.S. Patent No. 5,023,252. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

One preferred manner for administering a compound of the invention is inhalation. Inhalation is an effective means for delivering an agent directly to the respiratory tract. There are three general types of pharmaceutical inhalation devices: nebulizer inhalers, dry powder inhalers (DPI), and metered-dose inhalers (MDI). Nebulizer devices produce a stream of high velocity air that causes a therapeutic agent to spray as a mist which is carried into the patient's respiratory tract. The therapeutic agent is formulated in a liquid form such as a solution or a suspension of micronized particles of respirable size, where micronized is typically defined as having about 90 % or more of the particles with a diameter of less than about 10 μm. A typical formulation for use in a conventional nebulizer device is an isotonic aqueous solution of a pharmaceutical salt of the active agent at a concentration of the active agent of between about 0.05 μg/mL and about 10 mg/mL.

DPI's typically administer a therapeutic agent in the form of a free flowing powder that can be dispersed in a patient's air-stream during inspiration. In order to achieve a free flowing powder, the therapeutic agent can be formulated with a suitable excipient, such as lactose or starch. A dry powder formulation can be made, for example, by combining dry lactose having a particle size between about 1 μm and about 100 μm with micronized particles of a pharmaceutical salt of the active agent and dry blending. Alternative, the agent can be formulated without excipients. The formulation is loaded into a dry powder dispenser, or into inhalation cartridges or capsules for use with a dry powder delivery device.

Examples of DPI delivery devices provided commercially include Diskhaler (GlaxoSmithKline, Research Triangle Park, NC) (see, e.g., U.S. Patent No. 5,035,237); Diskus (GlaxoSmithKline) (see, e.g., U.S. Patent No. 6,378,519; Turbuhaler (AstraZeneca, Wilmington, DE) (see, e.g., U.S. Patent No. 4,524,769); and Rotahaler (GlaxoSmithKline) (see, e.g., U.S. Patent No. 4,353,365). Further examples of suitable DPI devices are described in U.S. Patent Nos. 5,415,162, 5,239,993, and 5,715,810 and references therein.

MDI's typically discharge a measured amount of therapeutic agent using compressed propellant gas. Formulations for MDI administration include a solution or suspension of active ingredient in a liquefied propellant. While chlorofluorocarbons, such as CCl_3F, conventionally have been used as propellants, due to concerns regarding adverse affects of such agents on the ozone layer, formulations using hydrofluoroalklanes (HFA), such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3,-heptafluoro-n-propane, (HFA 227) have been developed. Additional components of HFA formulations for MDI administration include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, and glycerin. (See, for example, U.S. Patent No. 5,225,183, EP 0717987 A2, and WO 92/22286.)

Thus, a suitable formulation for MDI administration can include from about 0.01 % to about 5 % by weight of a pharmaceutical salt of active ingredient, from about 0 % to about 20 % by weight ethanol, and from about 0 % to about 5 % by weight surfactant, with the remainder being the HFA propellant. In one approach, to prepare the formulation, chilled or pressurized hydrofluoroalkane is added to a vial containing the pharmaceutical salt of active compound, ethanol (if present) and the surfactant (if present). To prepare a suspension, the pharmaceutical salt is provided as micronized particles. The formulation is loaded into an aerosol canister, which forms a portion of an MDI device. Examples of MDI devices developed specifically for use with HFA propellants are provided in U.S. Patent Nos. 6,006,745 and 6,143,277.

In an alternative preparation, a suspension formulation is prepared by spray drying a coating of surfactant on micronized particles of a pharmaceutical salt of active compound. (See, for example, WO 99/53901 and WO 00/61108.) For additional examples of processes of preparing respirable particles, and formulations and devices suitable for inhalation dosing see U.S. Patent Nos. 6,268,533, 5,983,956, 5,874,063, and 6,221,398, and WO 99/55319 and WO 00/30614.

It will be understood that any form of the compounds of the invention, (i.e. free base, pharmaceutical salt, or solvate) that is suitable for the particular mode of administration, can be used in the pharmaceutical compositions discussed above.

The active compound is effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen

route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses of the therapeutic agent for inhalation administration are in the general range of from about 0.05 μg/day to about 1000 μg/day, preferably from about 0.5 μg/day to about 500 μg/day. A compound can be administered in a periodic dose: weekly, multiple times per week, daily, or multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several weeks or months, or the treatment regimen may require chronic administration. Suitable doses for oral administration are in the general range of from about 0.05 μg/day to about 100 mg/day, preferably 0.5 to 1000 μg/day.

The present active agents can also be co-administered with one or more other therapeutic agents. For example, for the treatment of asthma or of chronic obstructive pulmonary disease, the present agents can be administered in combination with a muscarinic receptor antagonist (e.g. ipatropium bromide or tiotropium) or a steroidal anti-inflammatory agent (e.g. fluticasone propionate, beclomethasone, budesonide, mometasone, ciclesonide, or triamcinolone). In addition, the present active agents can be co-administered with an agent having anti-inflammatory and/or bronchodilating or other beneficial activity, including but not limited to, a phosphodiesterase (PDE) inhibitor (e.g. theophylline); a PDE4 inhibitor (e.g. cilomilast or roflumilast); an immunoglobulin antibody (αIgE antibody); a leukotriene antagonist (e.g. monteleukast); a cytokine antagonist therapy, such as, an interleukin antibody (αIL antibody), specifically, an αIL-4 therapy, an αIL-13 therapy, or a combination thereof; a protease inhibitor, such as an elastase or tryptase inhibitor; cromolyn sodium; nedocromil sodium; and sodium cromoglycate. Further, the present agents can be co-administered with an antiinfective agent or antihistamines. Suitable doses for the other therapeutic agents administered in combination with a compound of the invention are in the range of about 0.05 μg/day to about 100 mg/day.

Accordingly, the compositions of the invention can optionally comprise a compound of the invention as well as another therapeutic agent as described above.

Additional suitable carriers for formulations of the active compounds of the present invention can be found in *Remington: The Science and Practice of Pharmacy, 20th*

Edition, Lippincott Williams & Wilkins, Philadelphia, PA, 2000. The following non-limiting examples illustrate representative pharmaceutical compositions of the invention.

Formulation Example A

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	2
Lactose, spray-dried	148
Magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Formulation Example B

This example illustrates the preparation of another representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	4
Cornstarch	50
Lactose	145
Magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

Formulation Example C

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention.

An oral suspension is prepared having the following composition.

Ingredients	
Active Compound	0.1 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.1 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Formulation Example D

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active Compound	0.2 g
Sodium Acetate Buffer Solution (0.4 M)	2.0 mL
HCl (1N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 mL

Formulation Example E

This example illustrates the preparation of a representative pharmaceutical composition for injection of a compound of this invention.

A reconstituted solution is prepared by adding 20 mL of sterile water to 1 g of the compound of this invention. Before use, the solution is then diluted with 200 mL of an intravenous fluid that is compatible with the active compound. Such fluids are chosen from 5% dextrose solution, 0.9% sodium chloride, or a mixture of 5% dextrose and 0.9% sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, Normosol-M and 5% dextrose, Isolyte E, and acylated Ringer's injection.

Formulation Example F

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation is prepared having the following composition:

Ingredients	
Active Compound	0.1-5.0 g
Hydroxypropyl-β-cyclodextrin	1-25 g
5% Aqueous Dextrose Solution (sterile)	q.s. to 100 mL

The above ingredients are blended and the pH is adjusted to 3.5 ± 0.5 using 0.5 N HCl or 0.5 N NaOH.

Formulation Example G

This example illustrates the preparation of a representative pharmaceutical composition for topical application of a compound of this invention.

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

Formulation Example H

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of the invention.

An aqueous aerosol formulation for use in a nebulizer is prepared by dissolving 0.1 mg of a pharmaceutical salt of active compound in a 0.9 % sodium chloride solution

acidified with citric acid. The mixture is stirred and sonicated until the active salt is dissolved. The pH of the solution is adjusted to a value in the range of from 3 to 8 by the slow addition of NaOH.

Formulation Example I

This example illustrates the preparation of a dry powder formulation containing a compound of the invention for use in inhalation cartridges.

Gelatin inhalation cartridges are filled with a pharmaceutical composition having the following ingredients:

Ingredients	mg/cartridge
Pharmaceutical salt of active compound	0.2
Lactose	25

The pharmaceutical salt of active compound is micronized prior to blending with lactose. The contents of the cartridges are administered using a powder inhaler.

Formulation Example J

This example illustrates the preparation of a dry powder formulation containing a compound of the invention for use in a dry powder inhalation device.

A pharmaceutical composition is prepared having a bulk formulation ratio of micronized pharmaceutical salt to lactose of 1:200. The composition is packed into a dry powder inhalation device capable of delivering between about 10 µg and about 100 µg of active drug ingredient per dose.

Formulation Example K

This example illustrates the preparation of a formulation containing a compound of the invention for use in a metered dose inhaler.

A suspension containing 5 % pharmaceutical salt of active compound, 0.5 % lecithin, and 0.5 % trehalose is prepared by dispersing 5 g of active compound as micronized particles with mean size less than 10 µm in a colloidal solution formed from 0.5 g of trehalose and 0.5 g of lecithin dissolved in 100 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a

mean diameter less than 1.5 μm. The particles are loaded into canisters with pressurized 1,1,1,2-tetrafluoroethane.

Formulation Example L

This example illustrates the preparation of a formulation containing a compound of the invention for use in a metered dose inhaler.

A suspension containing 5 % pharmaceutical salt of active compound and 0.1 % lecithin is prepared by dispersing 10 g of active compound as micronized particles with mean size less than 10 μm in a solution formed from 0.2 g of lecithin dissolved in 200 mL of demineralized water. The suspension is spray dried and the resulting material is micronized to particles having a mean diameter less than 1.5 μm. The particles are loaded into canisters with pressurized 1,1,1,2,3,3,3-heptafluoro-n-propane.

Biological Assays

The compounds of this invention, and their pharmaceutically-acceptable salts, exhibit biological activity and are useful for medical treatment. The ability of a compound to bind to the β_2 adrenergic receptor, as well as its selectivity, agonist potency, and intrinsic activity can be demonstrated using *in vitro* Tests A-C below, *in vivo* Test D, below, or can be demonstrated using other tests that are known in the art.

Abbreviations

%Eff	% efficacy
ATCC	American Type Culture Collection
BSA	Bovine Serum Albumin
cAMP	Adenosine 3':5'-cyclic monophosphate
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
Emax	maximal efficacy
FBS	Fetal bovine serum
Gly	Glycine
HEK-293	Human embryonic kidney - 293
PBS	Phosphate buffered saline
rpm	rotations per minute
Tris	Tris(hydroxymethyl)aminomethane

Membrane Preparation From Cells Expressing Human β_1 or β_2 Adrenergic Receptors

HEK-293 derived cell lines stably expressing cloned human β_1 or β_2 adrenergic receptors, respectively, were grown to near confluency in DMEM with 10% dialyzed FBS in the presence of 500 μg/mL Geneticin. The cell monolayer was lifted with Versene 1:5,000 (0.2 g/L EDTA in PBS) using a cell scraper. Cells were pelleted by centrifugation at 1,000 rpm, and cell pellets were either stored frozen at -80°C or membranes were prepared immediately. For preparation, cell pellets were resuspended in lysis buffer (10 mM Tris/HCL pH 7.4 @ 4°C, one tablet of "Complete Protease Inhibitor Cocktail Tablets with 2 mM EDTA" per 50 mL buffer (Roche cat.# 1697498, Roche Molecular Biochemicals, Indianapolis, IN)) and homogenized using a tight-fitting Dounce glass homogenizer (20 strokes) on ice. The homogenate was centrifuged at 20,000 x g, the pellet was washed once with lysis buffer by resuspension and centrifugation as above. The final pellet was resuspended in membrane buffer (75 mM Tris/HCl pH 7.4, 12.5mM $MgCl_2$, 1 mM EDTA @ 25°C). Protein concentration of the membrane suspension was determined by the method of Bradford (Bradford MM., *Analytical Biochemistry*, **1976**, *72*, 248-54). Membranes were stored frozen in aliquots at -80°C.

Test A

Radioligand Binding Assay on Human β_1 and β_2 Adrenergic Receptors

Binding assays were performed in 96-well microtiter plates in a total assay volume of 100 μL with 5 μg membrane protein for membranes containing the human β_2 adrenergic receptor, or 2.5 μg membrane protein for membranes containing the human β_1 adrenergic receptor in assay buffer (75 mM Tris/HCl pH 7.4 @ 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA). Saturation binding studies for determination of K_d values of the radioligand were done using [^{3}H]dihydroalprenolol (NET-720, 100 Ci/mmol, PerkinElmer Life Sciences Inc., Boston, MA) at 10 different concentrations ranging from 0.01 nM – 200 nM. Displacement assays for determination of pK_i values of compounds were done with [^{3}H]dihydroalprenolol at 1 nM and 10 different concentrations of compound ranging from 40 pM – 10 μM. Compounds were dissolved to a concentration of 10 mM in dissolving buffer (25 mM Gly-HCl pH 3.0 with 50% DMSO), then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer. Non-

specific binding was determined in the presence of 10 μM unlabeled alprenolol. Assays were incubated for 90 minutes at room temperature, binding reactions were terminated by rapid filtration over GF/B glass fiber filter plates (Packard BioScience Co., Meriden, CT) presoaked in 0.3% polyethyleneimine. Filter plates were washed three times with filtration buffer (75 mM Tris/HCl pH 7.4 @ 4°C, 12.5 mM $MgCl_2$, 1 mM EDTA) to remove unbound radioactivity. Plates were dried, 50 μL Microscint-20 liquid scintillation fluid (Packard BioScience Co., Meriden, CT) was added and plates were counted in a Packard Topcount liquid scintillation counter (Packard BioScience Co., Meriden, CT). Binding data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 3-parameter model for one-site competition. The curve minimum was fixed to the value for nonspecific binding, as determined in the presence of 10 μM alprenolol. K_i values for compounds were calculated from observed IC_{50} values and the K_d value of the radioligand using the Cheng-Prusoff equation (Cheng Y, and Prusoff WH., *Biochemical Pharmacology*, **1973**, *22*, 23, 3099-108). The receptor subtype selectivity was calculated as the ratio of $K_i(\beta_1)/K_i(\beta_2)$. All of the compounds tested demonstrated greater binding at the β_2 adrenergic receptor than at the β_1 adrenergic receptor, i.e. $K_i(\beta_1) > K_i(\beta_2)$. Most preferred compounds of the invention demonstrated a selectivity greater than about 20.

Test B

Whole-cell cAMP Flashplate Assay With a Cell Line Heterologously Expressing Human β_2 Adrenergic Receptor

For the determination of agonist potencies, a HEK-293 cell line stably expressing cloned human β_2 adrenergic receptor (clone H24.14) was grown to confluency in medium consisting of DMEM supplemented with 10% FBS and 500 μg/mL Geneticin. The day before the assay, antibiotics were removed from the growth-medium.

cAMP assays were performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with ^{125}I-cAMP (NEN SMP004, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturers instructions.

On the day of the assay, cells were rinsed once with PBS, lifted with Versene 1:5,000 (0.2 g/L EDTA in PBS) and counted. Cells were pelleted by centrifugation at 1,000 rpm and resuspended in stimulation buffer prewarmed to 37°C at a final concentration of 800,000 cells / mL. Cells were used at a final concentration of 40,000

cells / well in the assay. Compounds were dissolved to a concentration of 10 mM in dissolving buffer (25 mM Gly-HCl pH 3.0 with 50% DMSO), then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer (75 mM Tris/HCl pH 7.4 @ 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA). Compounds were tested in the assay at 10 different concentrations, ranging from 2.5 µM to 9.5 pM. Reactions were incubated for 10 min at 37°C and stopped by addition of 100 µl ice-cold detection buffer. Plates were sealed, incubated over night at 4°C and counted the next morning in a topcount scintillation counter (Packard BioScience Co., Meriden, CT). The amount of cAMP produced per mL of reaction was calculated based on the counts observed for the samples and cAMP standards, as described in the manufacturer's user manual. Data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 4-parameter model for sigmoidal dose-response with variable slope. Agonist potencies were expressed as pEC_{50} values. All of the compounds tested demonstrated activity at the β_2 adrenergic receptor in this assay, as evidenced by pEC_{50} values greater than about 5. Most preferred compounds of the invention demonstrated pEC_{50} values greater than about 7.

<u>Test C</u>

Whole-cell cAMP Flashplate Assay With a Lung Epithelial Cell Line Endogenously Expressing Human β_2 Adrenergic Receptor

For the determination of agonist potencies and efficacies (intrinsic activities) in a cell line expressing endogenous levels of β_2 adrenergic receptor, a human lung epithelial cell line (BEAS-2B) was used (ATCC CRL-9609, American Type Culture Collection, Manassas, VA) (January B, et al., *British Journal of Pharmacology,* 1998, *123,* 4, 701-11). Cells were grown to 75-90% confluency in complete, serum-free medium (LHC-9 MEDIUM containing Epinephrine and Retinoic Acid, cat # 181-500, Biosource International, Camarillo, CA). The day before the assay, medium was switched to LHC-8 (No epinephrine or retinoic acid, cat # 141-500, Biosource International, Camarillo, CA).

cAMP assays were performed in a radioimmunoassay format using the Flashplate Adenylyl Cyclase Activation Assay System with ^{125}I-cAMP (NEN SMP004, PerkinElmer Life Sciences Inc., Boston, MA), according to the manufacturers instructions.

On the day of the assay, cells were rinsed with PBS, lifted by scraping with 5mM EDTA in PBS, and counted. Cells were pelleted by centrifugation at 1,000 rpm and resuspended in stimulation buffer prewarmed to 37°C at a final concentration of 600,000

cells / mL. Cells were used at a final concentration of 30,000 cells / well in the assay. Compounds were dissolved to a concentration of 10 mM in dissolving buffer (25 mM Gly-HCl pH 3.0 with 50% DMSO), then diluted to 1 mM in 50 mM Gly-HCl pH 3.0, and from there serially diluted into assay buffer (75 mM Tris/HCl pH 7.4 @ 25°C, 12.5 mM $MgCl_2$, 1 mM EDTA, 0.2% BSA).

Compounds were tested in the assay at 10 different concentrations, ranging from 10 μM to 40 pM. Maximal response was determined in the presence of 10 μM Isoproterenol. Reactions were incubated for 10 min at 37°C and stopped by addition of 100 μl ice-cold detection buffer. Plates were sealed, incubated over night at 4°C and counted the next morning in a topcount scintillation counter (Packard BioScience Co., Meriden, CT). The amount of cAMP produced per mL of reaction was calculated based on the counts observed for samples and cAMP standards, as described in the manufacturer's user manual. Data were analyzed by nonlinear regression analysis with the GraphPad Prism Software package (GraphPad Software, Inc., San Diego, CA) using the 4-parameter model for sigmoidal dose-response with variable slope. Compounds of the invention tested in this assay demonstrated pEC_{50} values greater than about 7.

Compound efficacy (%Eff) was calculated from the ratio of the observed Emax (TOP of the fitted curve) and the maximal response obtained for 10μM isoproterenol and was expressed as %Eff relative to isoproterenol. The compounds tested demonstrated a %Eff greater than about 20.

Test D

Assay Of Bronchoprotection Against Acetylcholine-Induced Bronchospasm In A Guinea Pig Model

Groups of 6 male guinea pigs (Duncan-Hartley (HsdPoc:DH) Harlan, Madison, WI) weighing between 250 and 350 g were individually identified by cage cards. Throughout the study animals were allowed access to food and water *ad libitum*.

Test compounds were administered *via* inhalation over 10 minutes in a whole-body exposure dosing chamber (R&S Molds, San Carlos, CA). The dosing chambers were arranged so that an aerosol was simultaneously delivered to 6 individual chambers from a central manifold. Following a 60 minute acclimation period and a 10 minute exposure to nebulized water for injection (WFI), guinea pigs were exposed to an aerosol of test compound or vehicle (WFI). These aerosols were generated from

aqueous solutions using an LC Star Nebulizer Set (Model 22F51, PARI Respiratory Equipment, Inc. Midlothian, VA) driven by a mixture of gases (CO_2 = 5%, O_2 = 21% and N_2 = 74%) at a pressure of 22 psi. The gas flow through the nebulizer at this operating pressure was approximately 3 L/minute. The generated aerosols were driven into the chambers by positive pressure. No dilution air was used during the delivery of aerosolized solutions. During the 10 minute nebulization, approximately 1.8 mL of solution was nebulized. This was measured gravimetrically by comparing pre-and post-nebulization weights of the filled nebulizer.

The bronchoprotective effects of compounds administered *via* inhalation were evaluated using whole body plethysmography at 1.5, 24, 48 and 72 hours post-dose. Forty-five minutes prior to the start of the pulmonary evaluation, each guinea pig was anesthetized with an intramuscular injection of ketamine (43.75 mg/kg), xylazine (3.50 mg/kg) and acepromazine (1.05 mg/kg). After the surgical site was shaved and cleaned with 70% alcohol, a 2-5 cm midline incision of the ventral aspect of the neck was made. Then, the jugular vein was isolated and cannulated with a saline-filled polyethylene catheter (PE-50, Becton Dickinson, Sparks, MD) to allow for intravenous infusions of a 0.1 mg/mL solution of acetylcholine (Ach), (Sigma-Aldrich, St. Louis, MO) in saline. The trachea was then dissected free and cannulated with a 14G teflon tube (#NE- 014, Small Parts, Miami Lakes, FL). If required, anesthesia was maintained by additional intramuscular injections of the aforementioned anesthetic cocktail. The depth of anesthesia was monitored and adjusted if the animal responded to pinching of its paw or if the respiration rate was greater than 100 breaths/minute.

Once the cannulations were complete, the animal was placed into a plethysmograph (#PLY3114, Buxco Electronics, Inc., Sharon, CT) and an esophageal pressure cannula was inserted to measure pulmonary driving pressure (*pressure*). The teflon tracheal tube was attached to the opening of the plethysmograph to allow the guinea pig to breathe room air from outside the chamber. The chamber was then sealed. A heating lamp was used to maintain body temperature and the guinea pig's lungs were inflated 3 times with 4 mL of air using a 10 mL calibration syringe (#5520 Series, Hans Rudolph, Kansas City, MO) to ensure that the lower airways had not collapsed and that the animal did not suffer from hyperventilation.

Once it was determined that baseline values were within the range 0.3 - 0.9 mL/cm H_2O for compliance and within the range

0.1 - 0.199 cm H_2O/mL per second for resistance, the pulmonary evaluation was initiated. A Buxco pulmonary measurement computer progam enabled the collection and derivation of pulmonary values. Starting this program initiated the experimental protocol and data collection. The changes in volume over time that occured within the plethysmograph with each breath were measured *via* a Buxco pressure transducer. By integrating this signal over time, a measurement of *flow* was calculated for each breath. This signal, together with the pulmonary driving *pressure* changes, which were collected using a Sensym pressure transducer (#TRD4100), was connected *via* a Buxco (MAX 2270) preamplifier to a data collection interface (#'s SFT3400 and SFT3813). All other pulmonary parameters were derived from these two inputs.

Baseline values were collected for 5 minutes, after which time the guinea pigs were challenged with Ach. Ach was infused intravenously for 1 minute from a syringe pump (sp210iw, World Precision Instruments, Inc., Sarasota, FL) at the following doses and prescribed times from the start of the experiment: 1.9 μg/minute at 5 minutes, 3.8 μg/minute at 10 minutes, 7.5 μg/minute at 15 minutes, 15.0 μg/minute at 20 minutes, 30 μg/minute at 25 minutes and 60 μg/minute at 30 minutes. If resistance or compliance had not returned to baseline values at 3 minutes following each Ach dose, the guinea pig's lungs were inflated 3 times with 4 mL of air from a 10 mL calibration syringe. Recorded pulmonary parameters included respiration frequency (breaths/minute), compliance (mL/cm H_2O) and pulmonary resistance (cm H_2O/ mL per second) (Giles *et al.*, 1971). Once the pulmonary function measurements were completed at minute 35 of this protocol, the guinea pig was removed from the plethysmograph and euthanized by CO_2 asphyxiation.

The quantity PD_2, which is defined as the amount of Ach needed to cause a doubling of the baseline pulmonary resistance, was calculated using the pulmonary resistance values derived from the *flow* and the *pressure* over a range of Ach challenges using the following equation. This was derived from the equation used to calculate PC_{20} values in the clinic (Am. Thoracic Soc, 2000).

$$\mathbf{PD_2 = antilog\left[\log C_1 + \frac{(\log C_2 - \log C_1)(2R_0 - R_1)}{R_2 - R_1}\right]}$$

where:

C_1 = Second to last Ach concentration (concentration preceding C_2)

C_2 = Final concentration of Ach (concentration resulting in a 2-fold increase in pulmonary resistance (R_L))

R_0 = Baseline R_L value

R_1 = R_L value after C_1

R_2 = R_L value after C_2

Statistical analysis of the data was performed using a One-Way Analysis of Variance followed by post-hoc analysis using a Bonferroni / Dunn test. A *P*-value <0.05 was considered significant.

Dose-response curves were fitted with a four parameter logistic equation using GraphPad Prism, version 3.00 for Windows (GraphPad Software, San Diego, California)

Y = Min + (Max-Min)/(1 + 10^((log ED_{50}-X)* Hillslope)),

where X is the logarithm of dose, Y is the response (PD_2), and Y starts at Min and approaches asymptotically to Max with a sigmoidal shape.

Representative compounds of the invention were found to have significant bronchoprotective activity at time points beyond 24 hours post-dose.

The following synthetic examples are offered to illustrate the invention, and are not to be construed in any way as limiting the scope of the invention.

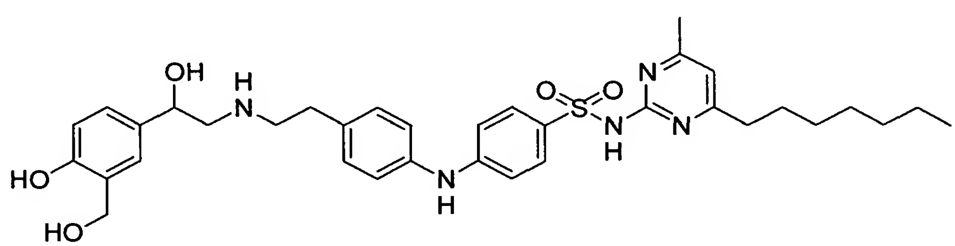
Examples

In the examples below, the following abbreviations have the following meanings. Any abbreviations not defined have their generally accepted meaning. Unless otherwise stated, all temperatures are in degrees Celsius.

Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl
DMSO	=	dimethyl sulfoxide
EtOAc	=	ethyl acetate
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
$MgSO_4$	=	anhydrous magnesium sulfate
NaHMDS	=	sodium hexamethyldisilazane
TMSCl	=	trimethylsilyl chloride
DMF	=	dimethyl formamide
Boc	=	*tert*-butoxycarbonyl
TBS	=	*tert*-butyldimethylsilyl

General: Unless noted otherwise, reagents, starting material and solvents were purchased from commercial suppliers, for example Sigma-Aldrich (St. Louis, MO), J. T. Baker (Phillipsburg, NJ), Honeywell Burdick and Jackson (Muskegon, MI), Trans World Chemicals, Inc. (TCI) (Rockville, MD), Mabybridge plc (Cornwall, UK), Peakdale Molecular Limited (High Peak, UK), Avocado Research Chemicals Limited (Lancashire, UK), and Bionet Research (Cornwall, UK) and used without further purification; reactions were run under nitrogen atmosphere; reaction mixtures were monitored by thin layer chromatography (silica TLC), analytical high performance liquid chromatography (anal. HPLC), or mass spectrometry; reaction mixtures were commonly purified by flash column chromatography on silica gel, or by preparative HPLC as described below; NMR samples were dissolved in deuterated solvent (CD_3OD, $CDCl_3$, or DMSO-*d6*), and spectra were acquired with a Varian Gemini 2000 instrument (300 MHz) using the residual protons of the listed solvent as the internal standard unless otherwise indicated; and mass spectrometric identification was performed by an electrospray ionization method (ESMS) with a Perkin Elmer instrument (PE SCIEX API 150 EX).

Example 1: Synthesis of compound 1

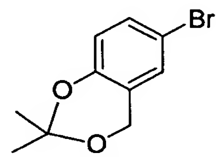


To 62 mg (0.1 mmol) of compound **bb** and 0.1 mmol of N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide (available from Sigma-Aldrich Library of Rare Chemicals) 0.15 mL of toluene were added 9.3 mg (0.015 mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (Aldrich) in 0.15 mL toluene, 4.6 mg (0.05 mmol) of tris(dibenzylidineacetone)dipalladium(0) (Aldrich) in 0.1 mL toluene, and 29 mg (0.3 mmol) of sodium tert-butoxide slurried in 0.4 mL toluene. The mixture was shaken and heated at 80°C for 5 hours. Acetic acid (80% aq., 0.6 mL) was added and the mixture was shaken and heated at 80°C for 5 hours. The crude reaction was diluted to a total volume of 2 mL with DMF, filtered, and purified by reversed phase HPLC, using a mass-triggered, automated collection device. The product containing fractions were

analyzed by analytical LC-MS, and freeze-dried to give a TFA salt of compound **1** as a powder.

The intermediate compound **bb** was prepared as follows.

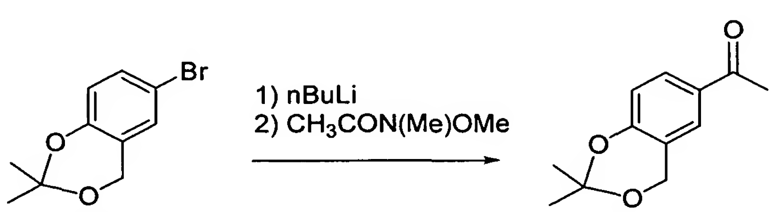
a. Synthesis of compound **xx**.



xx

To 5-bromo-2-hydroxybenzyl alcohol (93 g, 0.46 mol, available from Aldrich) in 2.0 L of 2,2-dimethoxypropane was added 700 mL of acetone, followed by 170 g of $ZnCl_2$. After stirring for 18 hours, 1.0 M aqueous NaOH was added until the aqueous phase was basic. 1.5 L of diethyl ether was added to the slurry, and the organic phase was decanted into a seporatory funnel. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **xx** as a light orange oil. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.28 (m, 2H), 6.75 (d, 1H), 4.79 (s, 2H), 1.44 (s, 6H).

b. Synthesis of compound **yy**

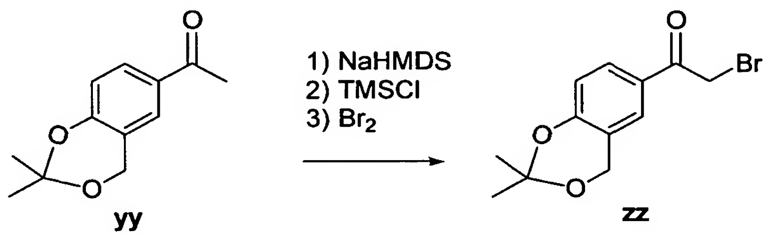


xx **yy**

To 110 g (0.46 mol) of compound **xx** in 1.0 L of THF at -78°C was added 236 mL (0.51 mol) of 2.14 M *n*-BuLi in hexanes via a dropping funnel. After 30 minutes, 71 g (0.69 mol) of *N*-Methyl-*N*-methoxyacetamide (available from TCI) was added. After 2 hours, the reaction was quenched with water, diluted with 2.0 L of 1.0 M aqueous phosphate buffer (pH=7.0), and extracted once with diethyl ether. The diethyl ether phase

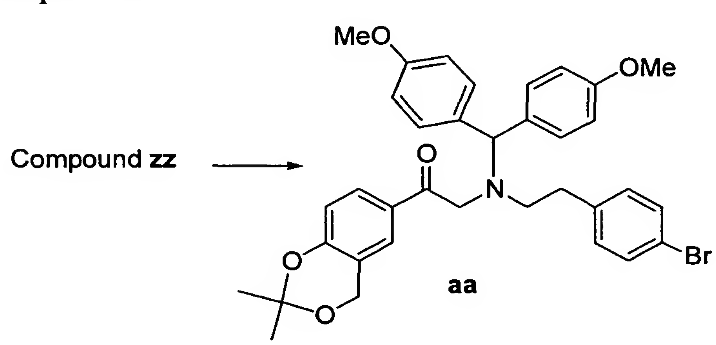
was washed once with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a light orange oil. The oil was dissolved in a minimum volume of ethyl acetate, diluted with hexanes, and the product crystallized to give compound **yy** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.65 (m, 1H), 6.85 (d, 1H), 4.88 (s, 2H), 2.54 (s, 3H), 1.56 (s, 6H).

c. Synthesis of compound **zz**.



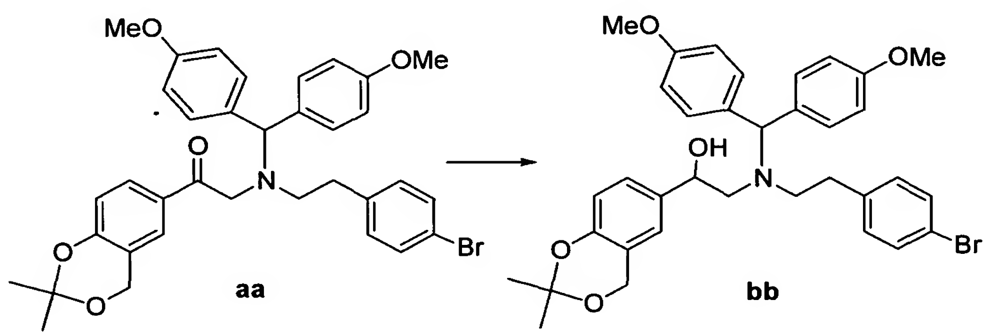
To 23.4 g (0.113 mol) of compound **yy** in 600 mL of THF at -78°C was added 135 mL of 1.0 M NaHMDS in THF (Aldrich). After 1 hour, 15.8 mL (0.124 mol) of TMSCl was added. After another 30 minutes, 5.82 mL (0.113 mol) of bromine was added. After a final 10 minutes, the reaction was quenched by diluting with diethyl ether and pouring onto 500 mL of 5% aqueous Na_2SO_3 premixed with 500 mL of 5% aqueous $NaHCO_3$. The phases were separated, and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give compound **zz** as a light orange oil that solidified in the freezer. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.69 (m, 1H), 6.88 (d, 1H), 4.89 (s, 2H), 4.37 (s, 2H), 1.56 (s, 6H).

d. Synthesis of compound **aa**.



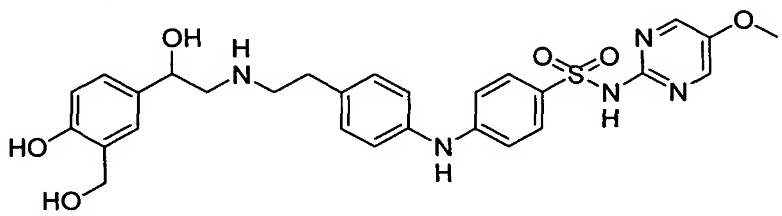
To 32 g (0.113 mol) of compound **zz** in 300 mL methylene chloride at 0°C was added 31.6 mL (0.23 mol) of triethylamine, followed by 16.0 mL (0.10 mol) of 4-bromophenethylamine (Aldrich). After 2 hours, 27 g (0.10 mol) of the 4,4'-dimethoxychlorodiphenylmethane was added. After 30 minutes, the slurry was partitioned between 50% saturated aqueous $NaHCO_3$ and diethyl ether, and the phases were separated. The organic phase was washed once each with water and brine, dried over K_2CO_3, filtered, and concentrated to an orange oil. The oil was purified by silica gel chromatography (1400 mL silica gel, eluted with 3 acetonitrile/0.5 triethylamine/96.5 methylene chloride) to give compound **aa** as a light orange foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.65 (m, 1H), 7.57 (m, 1H), 7.38 (d, 2H), 7.19 (d, 4H), 6.95 (d, 2H), 6.78 (m, 5H), 5.09 (s, 1H), 4.82 (s, 2H), 3.98 (s, 2H), 3.73 (m, 1H), 3.66 (s, 6H), 2.71 (m, 4H), 1.45 (s, 6H).

e. Synthesis of compound **bb**.



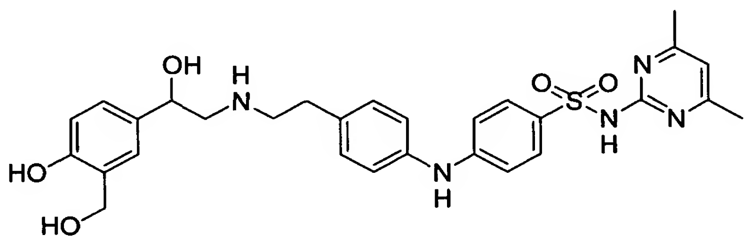
To 41 g (65 mmol) of compound **aa** in 120mL of THF was added 200 mL of methanol, followed by 2.46 g (65 mmol) of sodium borohydride. After 1 hour, the solution was partitioned between 1.0 M aqueous phosphate buffer (pH=7.0) and diethyl ether, and the phases were separated. The diethyl ether phase was washed with brine, dried over K_2CO_3, filtered, and concentrated to an oil. The oil was purified by silica gel chromatography (1200 mL silica gel, eluted with 18 acetone/0.5 triethylamine/81.5 hexanes) to give compound **bb** as a white foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.37 (d, 2H), 7.13 (m, 4H), 6.95-6.75 (m, 8H), 6.68 (d, 1H), 4.95 (d, 1H), 4.83 (s, 1H), 4.74 (s, 2H), 4.56 (m, 1H), 3.67 (2, 6H), 2.55 (m, 4H), 1.42 (s, 6H).

Example 2: Synthesis of compound 2



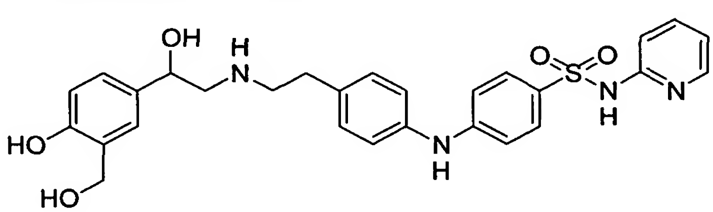
Using a coupling procedure similar to that described in Example 1, except replacing the *N*[1]-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with *N*[1]-(5-methoxy-2-pyrimidinyl)sulfanilamide (sulfameter, available from Aldrich), a TFA salt of compound **2** was prepared. *m/z*: [M + H$^+$] calcd for $C_{28}H_{31}N_5O_6S$ 566.2; found 566.2.

Example 3: Synthesis of compound 3



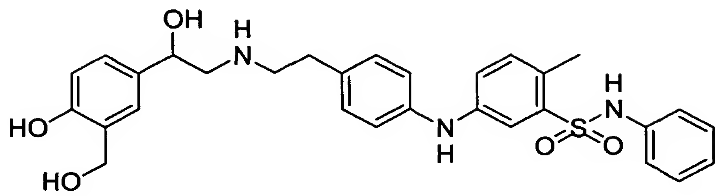
Using a coupling procedure similar to that described in Example 1, except replacing the *N*[1]-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with *N*[1]-(4,6-dimethyl-2-pyrimidinyl)sulfanylamide (sulfamethazine, available from Aldrich), a TFA salt of compound **3** was prepared. *m/z*: [M + H$^+$] calcd for $C_{29}H_{33}N_5O_5S$ 564.2; found 564.2.

Example 4: Synthesis of compound 4



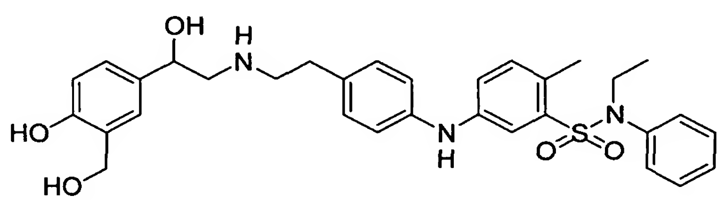
Using a coupling procedure similar to that described in Example 1, except replacing the *N*[1]-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 2-sulfanilamidopyrimidine (sulfapyridine, available from Aldrich), a TFA salt of compound **4** was prepared. *m/z*: [M + H$^+$] calcd for $C_{28}H_{30}N_4O_5S$ 535.2; found 535.2.

Example 5: Synthesis of compound 5



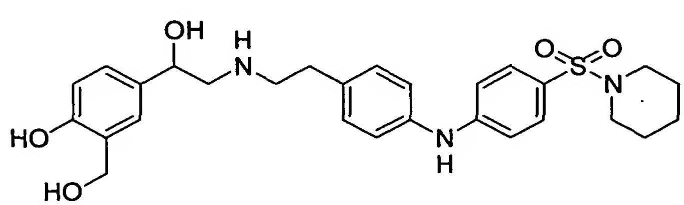
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 5-amino-ortho-toluenesulfonanilide (p-toluidine-o-sulfanilide, available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **5** was prepared. *m/z*: [M + H^+] calcd for $C_{30}H_{33}N_3O_5S$ 548.2; found 548.2.

Example 6: Synthesis of compound 6



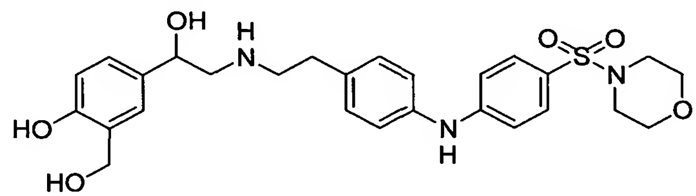
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-aminotoluene-2-sulfethylanilide (available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **6** was prepared. *m/z*: [M + H^+] calcd for $C_{32}H_{37}N_3O_5S$ 576.3; found 576.2.

Example 7: Synthesis of compound 7



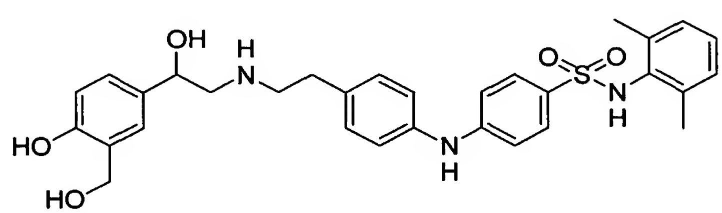
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(piperidinosulfonyl)aniline (available from Maybridge), a TFA salt of compound **7** was prepared. *m/z*: [M + H$^+$] calcd for $C_{28}H_{35}N_3O_5S$ 526.2; found 526.2.

Example 8: Synthesis of compound 8



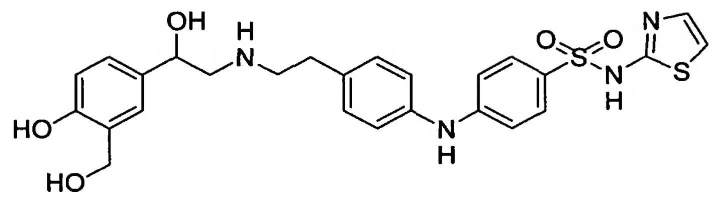
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(morpholinosulfonyl)aniline (available from Maybridge), a TFA salt of compound **8** was prepared. *m/z*: [M + H$^+$] calcd for $C_{27}H_{33}N_3O_6S$ 528.2; found 528.2.

Example 9: Synthesis of compound 9



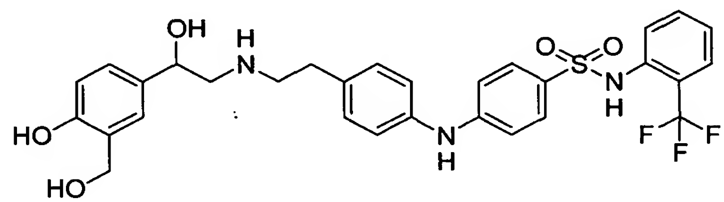
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with N^1-(2,6-dimethylphenyl)-4-aminobenzene-1-sulfonamide (available from Maybridge), a TFA salt of compound **9** was prepared. *m/z*: [M + H$^+$] calcd for $C_{31}H_{35}N_3O_5S$ 562.2; found 562.2.

Example 10: Synthesis of compound 10



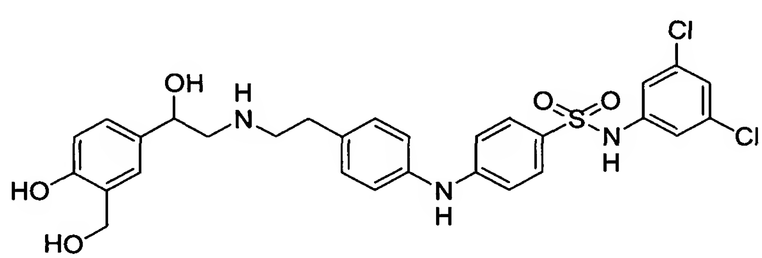
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with N^1-(2-thiazolyl)sulfanilamide (sulfathiazole, available from Aldrich), a TFA salt of compound **10** was prepared.

Example 11: Synthesis of compound 11



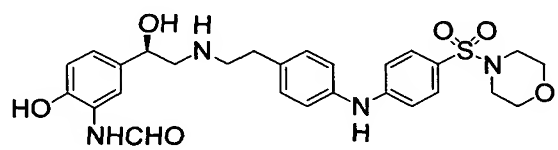
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with N^1-[2-(trifluoromethyl)phenyl]-4-aminobenzene-1-sulfonamide (available from Maybridge), a TFA salt of compound **11** was prepared.

Example 12: Synthesis of compound 12



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with N^1-(3,5-dichlorophenyl)-4-aminobenzene-1-sulfonamide (available from Maybridge), a TFA salt of compound **12** was prepared.

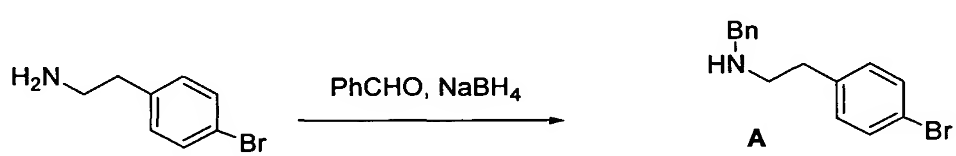
Example 13: Synthesis of compound 13



To a mixture of 0.69 g (1.83 mmol) of crude compound **ee** in 4 mL of methanol was added 70 mg of 10% palladium on carbon under a stream of nitrogen and the reaction was shaken under 50 psi H_2 for 2 days. The reaction was filtered and the residue was purified by reversed phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **13** as a powder. *m/z*: [M + H^+] calcd for $C_{27}H_{32}N_4O_6S$ 541.2; found 541.5.

The intermediate compound **ee** was prepared as follows.

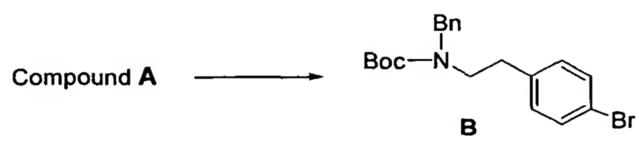
a. Synthesis of compound **A**.



To 10.7 g (53.0 mmol) of 4-bromophenethylamine (available from Aldrich) in 100 mL of toluene was added 6.80 g (64 mmol) of benzaldehyde. After stirring for 10 minutes, the cloudy mixture was concentrated under reduced pressure. The residue was re-concentrated twice from toluene, and the clear oil was dissolved in 50 mL of tetrahydrofuran. 2.0 g (53 mmol) of sodium borohydride was added to the solution, followed by 20 mL of methanol, and the flask was stirred in a water bath at ambient

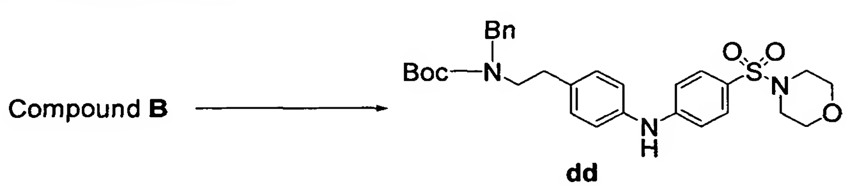
temperature for one hour. 1.0 M aqueous HCl was added until the pH was below 1. The slurry was stirred in an ice bath for 30 minutes, and the solids were isolated by filtration, rinsed with cold water, and air dried to give the hydrochloride salt of compound **A** as a colorless solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.40 (s, 2H), 7.50-7.32 (m, 7H), 7.14 (d, 2H), 4.07 (s, 2H), 3.03 (m, 2H), 2.92 (m, 2H).

b. Synthesis of compound **B**.



To 5.0 g (15 mmol) of compound **A** in 100 mL of methanol was added 1.70 g (16.5 mmol) of triethylamine. The solution was cooled in an ice/water bath, and 3.66 g (16.8 mmol) of di-tert-butyldicarbonate was added. After 3.5 hours, the solution was concentrated under reduced pressure, and the residue was partitioned between 1.0 M aqueous $NaHSO_4$ and diethyl ether, and the phases were separated. The diethyl ether phase was washed with water followed by brine, dried over Na_2SO_4, filtered, and concentrated to give compound **B** (6.1 g, 93%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.38 (d, 2H), 7.28-7.13 (m, 5H), 7.04 (m, 2H), 4.29 (br s, 2H), 3.20 (m, 2H), 2.62 (m, 2H), 1.25 (s, 9H).

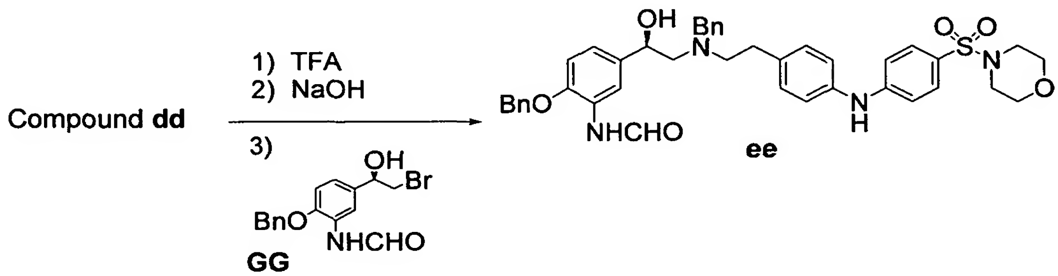
c. Synthesis of compound **dd**.



To a flask containing 3.4 g (8.8 mmol) of compound **B**, 2.8 g (11 mmol) of 4-morpholinosulfonyl)aniline (available from Maybridge), 0.41g (0.45mmol) of tris(dibenzylidineacetone)dipalladium(0), 0.83 g (1.3 mmol) of rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 1.1 g (11 mmol) of sodium tert-butoxide was added 40mL of toluene, and the mixture was heated at 95°C for 6 h under a nitrogen

atmosphere. The mixture was diluted with 200 mL diethyl ether and washed twice with 100 mL portions of 1.0 M aqueous $NaHSO_4$, followed by 100 mL of saturated aqueous $NaHCO_3$. The diethyl ether phase was dried over $MgSO_4$, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography (gradient of 30 to 40% ethyl acetate in hexanes) to afford compound **dd** as a yellow foam (2.5 g, 51%).

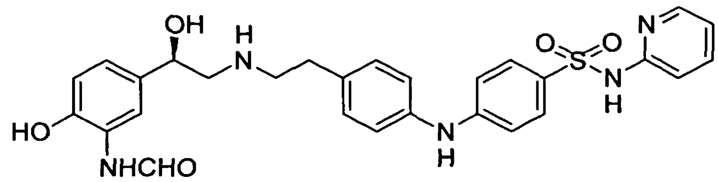
d. Synthesis of compound **ee**.



To 0.56 g of compound **dd** (.6 mmol) in 6 mL CH_2Cl_2 was added 4 mL TFA. After 15 minutes, the solution was concentrated, diluted with 30 mL ethyl acetate and washed twice with 1.0 N aqueous sodium hydroxide. The ethyl acetate layer was dried over $MgSO_4$, filtered, and concentrated to an oil and dissolved in 8 mL of 1:1 methanol:THF. Bromohydrin **GG** (340 mg, 0.96 mmol) and K_2CO_3 (370 mg, 2.7 mmol) were added and the reaction was stirred at room temperature for 1.5 h. The reaction was concentrated and the residue was diluted with 30 mL water and extracted twice with 30 mL portions of toluene. The toluene extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was heated to 120°C. After 13 h, the reaction was cooled to room temperature and the crude compound **dd** was carried on to the next step without purification.

The intermediate bromohydrin **GG** can be prepared as described in United States Patent Number 6,268,533 B1; and in R. Hett et al., *Organic Process Research and Development*, **1998**, *2*, 96-99. The intermediate bromohydrin **GG** can also be prepared using procedures similar to those described by Hong et al., *Tetrahedron Lett.*, **1994**, *35*, 6631; or similar to those described in United States Patent Number 5,495,054.

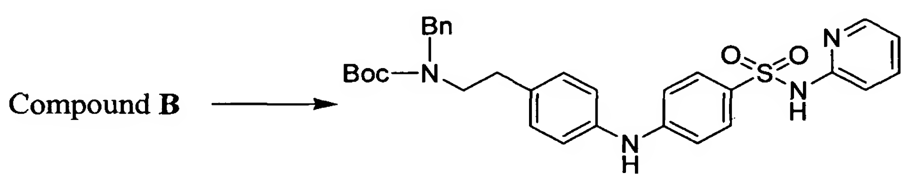
Example 14: Synthesis of compound 14



To a mixture of 0.6 g (0.83 mmol) of compound **ii** in 25 mL of ethanol was added 200 mg of 10% palladium on carbon under a stream of nitrogen and the reaction was allowed to stir under H_2 at atmospheric pressure for 5 days. The reaction was filtered and the residue was purified by reversed phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **14** as a powder. *m/z*: [M + H^+] calcd for $C_{28}H_{29}N_5O_5S$ 548.2; found 548.3.

The intermediate **ii** was prepared as follows.

a. Synthesis of compound **hh**.

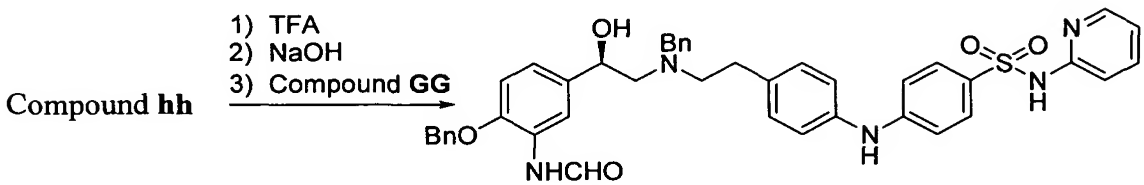


hh

To a flask containing 3.4 g (8.8 mmol) of compound **B** (Example 13, part b), 2.0 g (8.0 mmol) of sulfapyridine (available from Aldrich), 0.37 g (0.40 mmol) of tris(dibenzylidineacetone)dipalladium(0), 0.75 g (1.2 mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 2.31 g (24.0 mmol) of sodium tert-butoxide was added 40 mL of toluene, and the mixture was heated at 90°C for 18 h under a nitrogen atmosphere. The mixture was diluted with 200 mL methylene chloride and washed with 100 mL of saturated aqueous $NaHCO_3$, followed by 100 mL saturated aqueous NaCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The

oil was purified by silica gel chromatography (gradient of 0 to 5% methanol in methylene chloride) to afford compound **hh** as an orange solid.

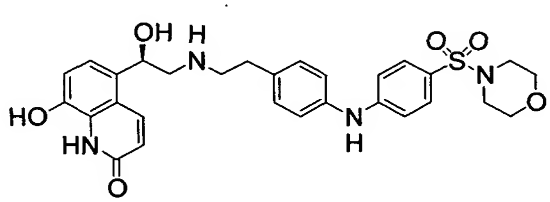
b. Synthesis of compound **ii**.



ii

To 4.5 g of compound **hh** (8.1 mmol) in 20 mL CH_2Cl_2 was added 1.5 mL TFA. After 1 hour, the solution was concentrated, basified with 1.0 N aqueous sodium hydroxide and extracted twice with methylene chloride, followed by an extraction using ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was purified by silica gel chromatography (gradient of 2 to 10% methanol in methylene chloride). The purified product was dissolved in 10 mL of 1:1 methanol:THF. Bromohydrin **GG** (Example 13, part d) (364 mg, 1.04 mmol) and K_2CO_3 (378 mg, 2.73 mmol) were added and the reaction was stirred at room temperature for 1.5 h. The reaction was concentrated and the residue was diluted with 30 mL water and extracted twice with 30 mL portions of toluene. The toluene extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was heated to 120°C. After 2 h, the reaction was cooled to room temperature and the crude compound was purified by silica gel chromatography (gradient of 5 to 10% methanol in methylene chloride) to afford compound **ii** as a tan solid.

Example 15: Synthesis of compound 15

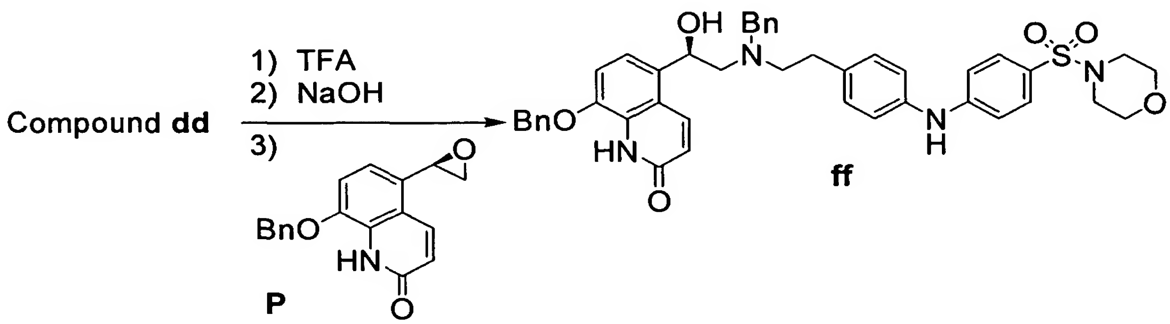


To 610 mg of compound **ff** (0.82 mmol) in 5.0 mL acetic acid was added 92 mg of 10% palladium on carbon. The reaction mixture was shaken under 40 psi H_2 for 20h.

The mixture was filtered and the filtrate was purified by reversed phase HPLC (gradient of 10 to 40% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **15** as a powder.
m/z: [M + H$^+$] calcd for $C_{29}H_{32}N_4O_6S$ 565.2; found 565.3.

The intermediate compound **ff** was prepared as follows.

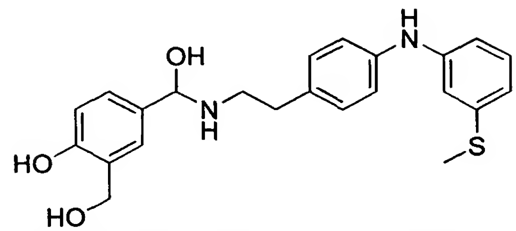
a. Synthesis of compound **ff**.



To 0.91 g of compound **dd** (1.6 mmol, Example 13, part c) in 8 mL CH_2Cl_2 was added 6 mL TFA. After 15 minutes, the solution was concentrated, diluted with 30 mL ethyl acetate and washed twice with 1.0 N aqueous sodium hydroxide. The ethyl acetate layer was dried over $MgSO_4$, filtered, and concentrated to a brown oil. The oil was dissolved in 6.0 mL of isopropanol and 375 mg (1.3 mmol) of epoxide **P** were added. The solution was heated to 70 °C. After 24 h, the solution was concentrated and the product purified by silica gel chromatography (3% methanol in CH_2Cl_2). Pure fractions were combined and concentrated to afford compound **ff** as a yellow foam.

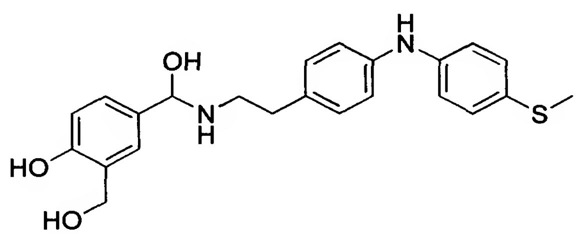
The intermediate epoxide **P** can be prepared as described in International Patent Application Publication Number WO 95/25104; and as described in EP 0 147 719 A2 and EP 0 147 791 B.

Example 16: Synthesis of compound 16



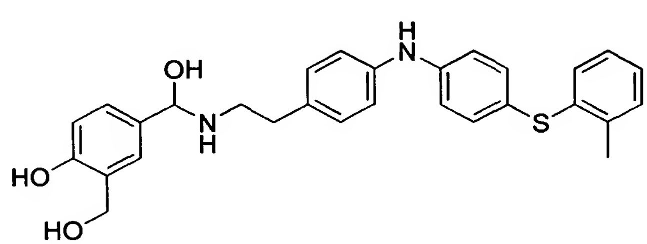
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-(methylthio)aniline (available from Aldrich), a TFA salt of compound **16** was prepared. *m/z*: [M + H$^+$] calcd for $C_{24}H_{28}N_2O_3S$ 425.2; found 425.1.

Example 17: Synthesis of compound 17



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(methylthio)aniline (available from Aldrich), a TFA salt of compound **17** was prepared. *m/z*: [M + H$^+$] calcd for $C_{24}H_{28}N_2O_3S$ 425.2; found 425.1.

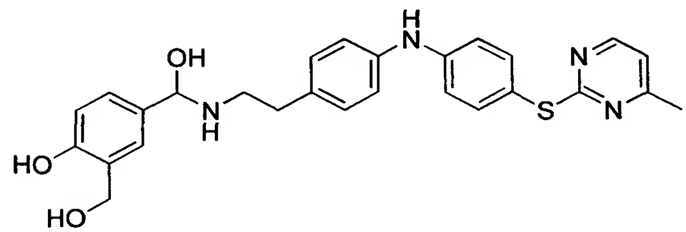
Example 18: Synthesis of compound 18



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide 4-(m-tolylthio)aniline

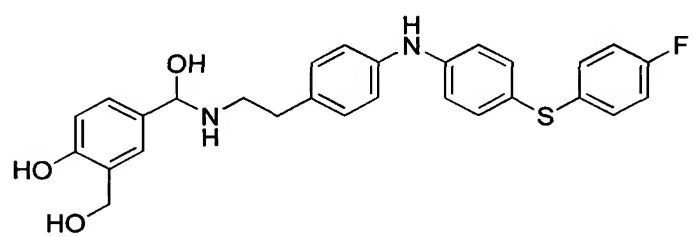
(available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **18** was prepared. *m/z*: [M + H$^+$] calcd for $C_{30}H_{32}N_2O_3S$ 501.2; found 501.2.

Example 19: Synthesis of compound 19



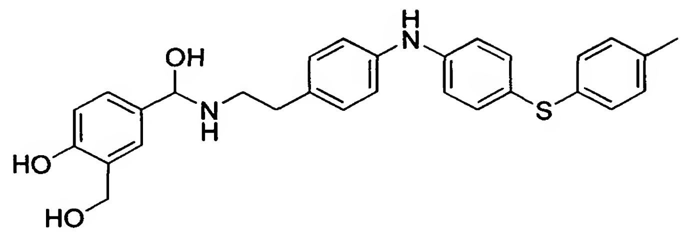
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-[(4-methylpyrimidin-2-yl)thio]benzeneamine (available from Peakdale), a TFA salt of compound **19** was prepared. *m/z*: [M + H$^+$] calcd for $C_{28}H_{30}N_4O_3S$ 503.2; found 503.1.

Example 20: Synthesis of compound 20



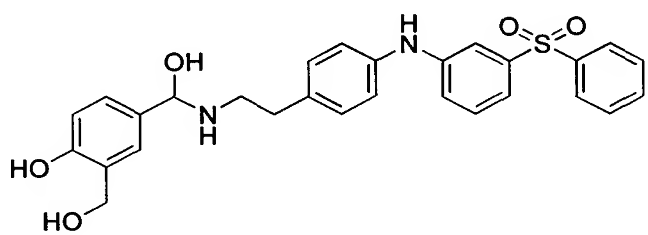
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-[(4-fluorophenyl)sulfonyl]aniline (available from Bionet), a TFA salt of compound **20** was prepared.

Example 21: Synthesis of compound 21



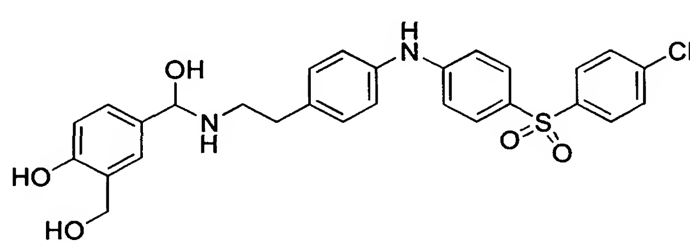
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-[(4-methylphenyl)sulfonyl]aniline (available from Bionet), a TFA salt of compound **21** was prepared.

Example 22: Synthesis of compound 22



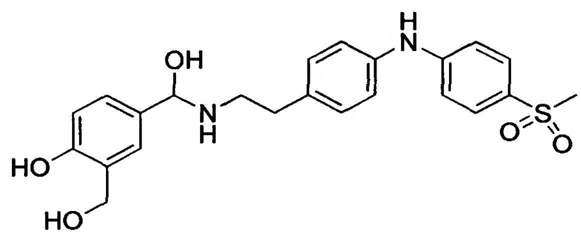
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-aminodiphenyl sulfone (available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **22** was prepared. *m/z*: [M + H^+] calcd for $C_{29}H_{30}N_2O_5S$ 519.2; found 519.2.

Example 23: Synthesis of compound 23



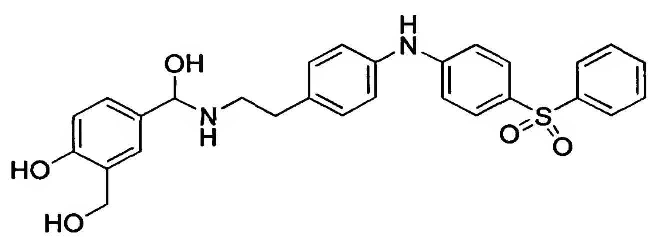
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(4-chloro-benzenesulfonyl)-phenylamine (available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **23** was prepared. *m/z*: [M + H$^+$] calcd for $C_{29}H_{29}ClN_2O_5S$ 553.2; found 553.1.

Example 24: Synthesis of compound 24



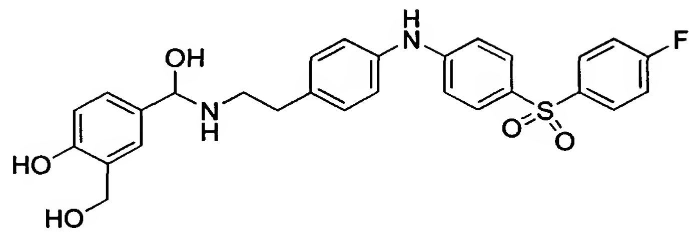
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(methylsulfonyl)aniline (available from Maybridge), a TFA salt of compound **24** was prepared. *m/z*: [M + H$^+$] calcd for $C_{24}H_{28}N_2O_5S$ 457.2; found 457.1.

Example 25: Synthesis of compound 25



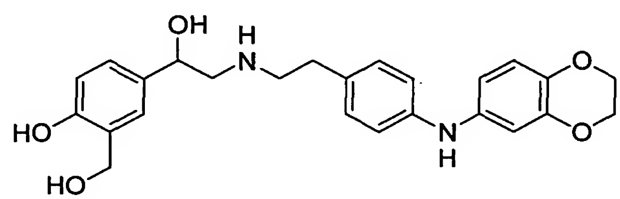
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(phenylsulfonyl)aniline (available from Maybridge), a TFA salt of compound **25** was prepared. *m/z*: [M + H$^+$] calcd for $C_{29}H_{30}N_2O_5S$ 519.2; found 519.2.

Example 26: Synthesis of compound 26



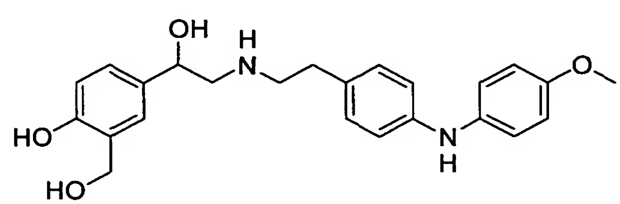
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-[(4-fluorophenyl)sulfonyl]aniline (available from Maybridge), a TFA salt of compound **26** was prepared. *m/z*: [M + H^+] calcd for $C_{29}H_{29}FN_2O_5S$ 537.2; found 537.1.

Example 27: Synthesis of compound 27



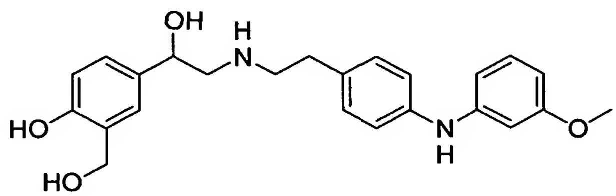
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3,4-ethylenedioxyaniline (available from Aldrich), a TFA salt of compound **27** was prepared.

Example 28: Synthesis of compound 28



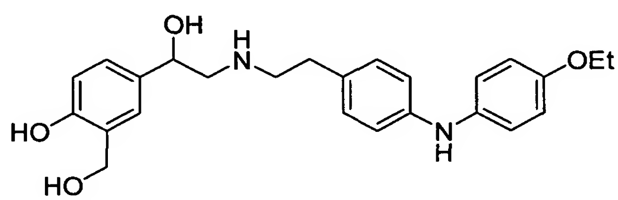
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-methoxyaniline (p-anisidine, available from Aldrich), a TFA salt of compound **28** was prepared.

Example 29: Synthesis of compound 29



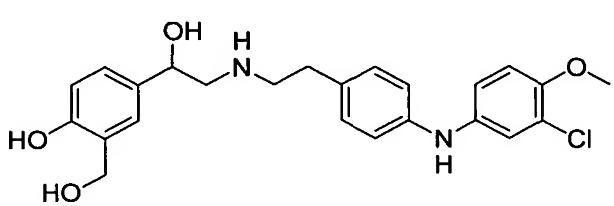
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-ethoxyaniline (m-anisidine, available from Aldrich), a TFA salt of compound **29** was prepared.

Example 30: Synthesis of *N*-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (30)



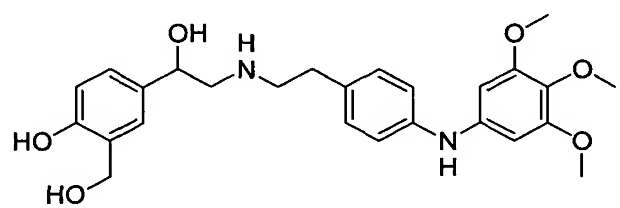
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 1-amino-4-ethoxybenzene (p-phenetidine, available from Aldrich), a TFA salt of compound **30** was prepared.

Example 31: Synthesis of compound 31



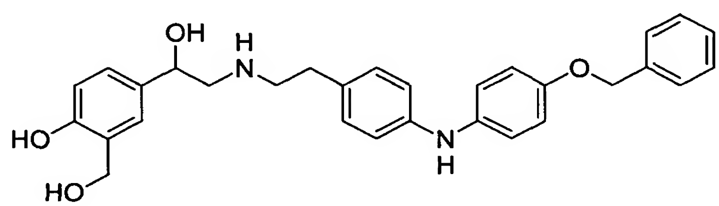
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-chloro-4-methoxyaniline (available from Aldrich), a TFA salt of compound **31** was prepared.

Example 32: Synthesis of compound 32



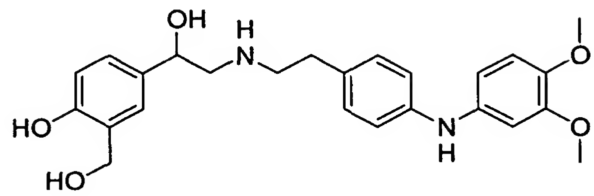
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3,4,5-trimethoxyaniline (available from Aldrich), a TFA salt of compound **32** was prepared. *m/z*: [M + H$^+$] calcd for $C_{26}H_{32}N_2O_6$ 469.2; found 469.2.

Example 33: Synthesis of compound 33



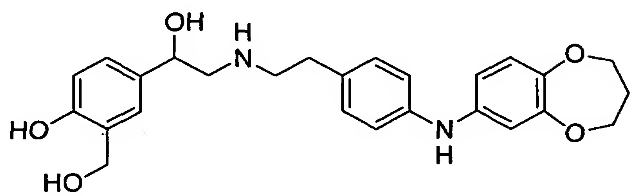
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-benzyloxyaniline hydrochloride (available from Aldrich), a TFA salt of compound **33** was prepared. *m/z*: [M + H$^+$] calcd for $C_{30}H_{32}N_2O_4$ 485.2; found 485.2.

Example 34: Synthesis of compound 34



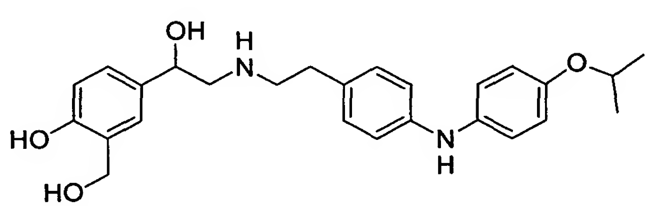
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3,4-dimethoxyaniline (available from Aldrich), a TFA salt of compound **34** was prepared. *m/z*: [M + H$^+$] calcd for $C_{25}H_{30}N_2O_5$ 439.2; found 439.2.

Example 35: Synthesis of compound 35



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3,4-(trimethylenedioxy)aniline (available from Maybridge), a TFA salt of compound **35** was prepared. *m/z*: [M + H$^+$] calcd for $C_{26}H_{30}N_2O_5$ 451.2; found 451.2.

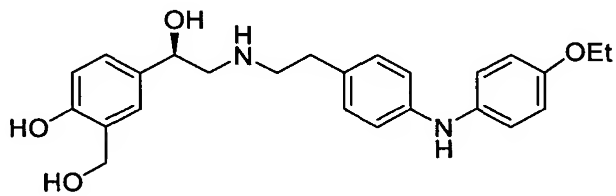
Example 36: Synthesis of compound 36



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with

4-isopropoxyaniline (available from TCI America), a TFA salt of compound **36** was prepared.*m/z*: [M + H$^+$] calcd for $C_{26}H_{32}N_2O_4$ 437.2; found 437.2.

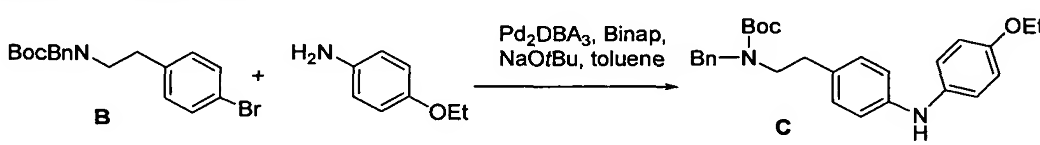
Example 37: Synthesis of *N*-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (37)



To a mixture of 3.0g (4.98mmol) of compound **F**, prepared in part c below, in 70ml of ethanol was added 1.0g of 10% Palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 1.5 hours. The reaction was filtered through celite, using methanol to rinse, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 40ml of 1/1 isopropanol / methanol , 2.74 ml of 4M HCl in dioxane was added, and the product was precipitated as the di-HCl salt by adding the solution to a large volume of EtOAc. The solids were isolated by filtration to give the di-HCl salt of compound **37** as a white solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.94 (br s, 1H), 8.63 (br s, 1H), 6.97-6.67 (m, 11H), 4.76 (m, 1H), 4.39 (s, 2H), 4.29 (br, 4H), 3.87 (dd, 2H), 3.02-2.76 (m, 6H), 1.22 (t, 3H). *m/z*: [M + H$^+$] calcd for $C_{25}H_{30}N_2O_4$ 423.2; found 423.2.

The intermediate compound **F** was prepared as follows.

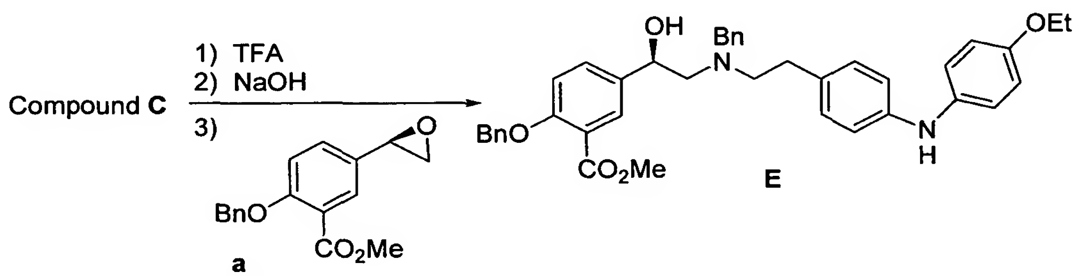
a. Synthesis of compound **C**.



To a flask containing 3.0 g (7.7 mmol) of compound **B**, 1.26g (9.1 mmol, Example 13, part b) of para-phenetidine (4-ethoxyaniline, available from Aldrich), 0.32 g (0.35 mmol) of tris(dibenzylidineacetone)dipalladium(0), 0.65 g (1.05mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 0.88 g (9.1 mmol) of sodium tert-

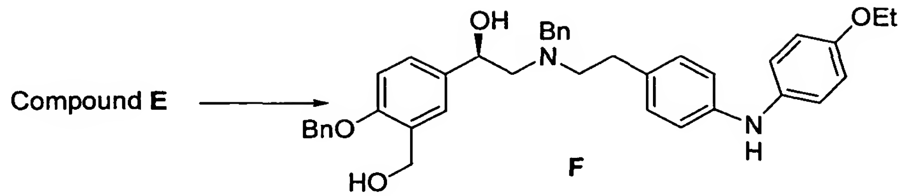
butoxide was added 35 ml of toluene, and the mixture was heated at 95°C for 5.5 hours under a nitrogen atmosphere. The mixture was partitioned between 1.0 M aqueous $NaHSO_4$ and diethyl ether, and the phases were separated. The diethyl ether phase was diluted with one volume of hexanes, and was washed once each with 1.0 M aqueous $NaHSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated to a dark oil. The oil was purified by chromatography, using 15% EtOAc / 85% hexanes as eluent, to give 2.52 g (73%) of compound **C** as a dark orange oil. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.64 (s, 1H), 7.28-7.13 (m,5H), 6.91-6.72 (m, 8H), 4.27 (s, 2H), 3.92 (q, 2H), 3.25 (s, 2H), 3.15 (m, 2H), 2.52 (m, 2H), 1.31 (s, 9H), 1.21 (t, 3H). *m/z*: [M + H$^+$] calcd for $C_{28}H_{34}N_2O_3$ 447.3; found 447.8.

b. Synthesis of compound **E**.



To 2.93g (6.56 mmol) of compound **C** in 15 ml of CH_2Cl_2 at 0°C was added 15 ml of trifluoroacetic acid. After 40 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between 1M NaOH and EtOAc. The phases were separated, and the EtOAc phase was washed once each with water and brine, dried over Na_2SO_4, filtered, and concentrated to an orange oil. The oil was dissolved in 20 ml of isopropanol, 1.86 g (6.56 mmol) of the epoxide **a** was added, and the solution was heated at 78°C overnight. The mixture was cooled to room temperature, and concentrated under reduced pressure to give compound **E** as an orange oil that was used without purification in the next step.

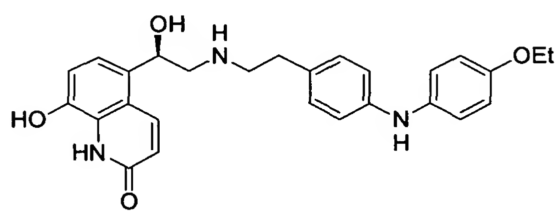
c. Synthesis of compound **F**.



To 6.56 mmol of crude compound **E** from the previous step in 40 mL of tetrahydrofuran at 0°C was added 16.4 mL (16.4 mmol) of 1M lithium aluminum hydride in tetrahydrofuran. After 2 hours, the reaction was quenched by slow addition of sodium sulfate decahydrate. The slurry was diluted with diethyl ether, dried over Na_2SO_4, filtered, and concentrated to an orange oil. The oil was purified by chromatography, using 50% EtOAc / 50% hexanes as eluent, to give compound **F** as an off-white foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.61 (s, 1H), 7.37-6.71 (m, 21H), 5.02 (s, 2H), 4.94 (m, 1H), 4.67 (m, 1H), 4.55 (m, 1H), 4.48 (d, 2H), 3.85 (dd, 2H), 3.63 (dd, 2H), 2.53 (m, 6H), 1.21 (t, 3H).

The intermediate epoxide **a** can be prepared as described by R. Hett et al., *Tetrahedron Lett.*, **1994**, *35*, 9357-9378.

Example 38: Synthesis of *N*-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (38)

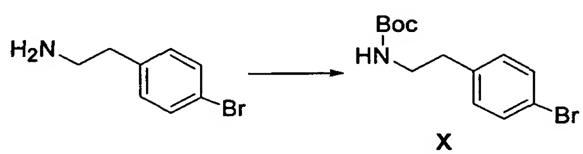


To a solution of 200 mg of compound **Q** (0.36 mmol) in 5.0 mL methanol was added 45 mg of 10% palladium on carbon. The reaction was placed under 1 atm H_2 gas. After 20 h, an additional 25 mg of 10% palladium on carbon was added and the reaction was stirred under 1 atm H_2 for an additional 24 h after which time the reaction was filtered. The filtrate was concentrated and purified by reversed phase preparative HPLC (gradient of 15-50% acetonitrile in 0.1 % TFA). Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **6** as a powder. A sample of

the TFA salt (39.7 mg) was dissolved in acetonitrile (1.0 mL), diluted with water (2.0 mL) and then 0.1 N HCl (5.0 mL). The solution was frozen and lyophilized to afford the hydrochloride salt of compound **38** (38.3 mg) as a yellow powder. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.5 (br s, 2H), 9.20 (br s, 1H), 8.75 (br s, 1H), 8.22 (d, 1H) 7.15 (d, 1H), 6.95-7.05 (m, 5H), 6.80-6.90 (m, 4H), 6.56 (d, 1H), 5.40 (dd, 1H), 3.95 (quar, 2H), 2.95-3.18 (m, 4H), 2.80-2.95 (m, 2H), 1.29 (t, 3H) ; *m/z*: [M + H$^+$] calcd for $C_{27}H_{29}N_3O_4$ 460.22; found 460.2.

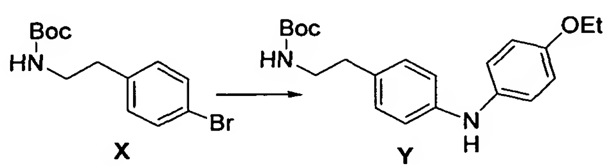
The intermediate compound **Q** was prepared as follows.

a. Synthesis of compound **X**.



To 7.03 g (35.1 mmol) of 4-bromophenethylamine (Sigma-Aldrich) in 60 mL of THF was added 8.6 g (39.4 mmol) of di-*tert*-butyldicarbonate. After 10 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give compound **X** as a white solid.

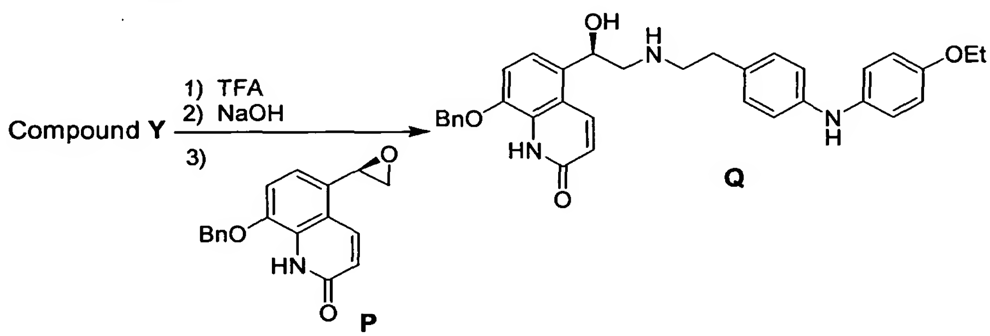
b. Synthesis of compound **Y**.



To a flask containing 1.2 g (4.1 mmol) of compound **X**, 0.72g (5.3 mmol) of para-phenetidine (4-ethoxyaniline, Sigma-Aldrich), 0.19 g (0.35 mmol) of tris(dibenzylidineacetone)dipalladium(0), 0.38 g (0.61 mmol) of rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 0.51 g (5.3 mmol) of sodium *tert*-butoxide,

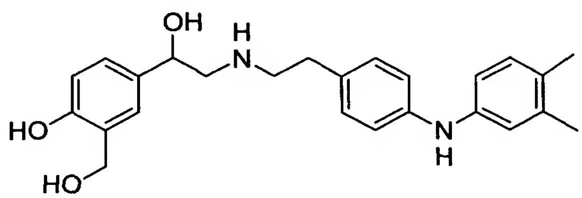
was added 35 mL of toluene, and the mixture was heated at 95°C for 16 hours under an nitrogen atmosphere. The mixture was partitioned between 1.0 M aqueous $NaHSO_4$ and diethyl ether. The diethyl ether phase was washed once each with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography, using 15% EtOAc / 85% hexanes as eluant, to give compound **Y** as a dark orange oil.

c. Synthesis of compound **Q**.



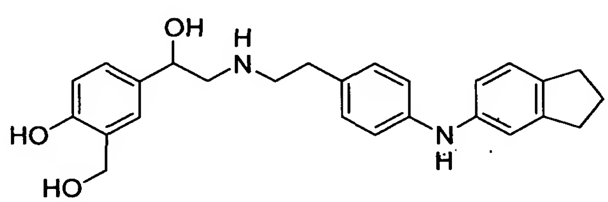
To 1.0 g of compound **Y** (2.8 mmol) in 5 mL CH_2Cl_2 was added 4 mL TFA. After 15 minutes, the solution was concentrated, diluted with 50 mL isopropyl acetate and washed twice with 1.0 M aqueous NaOH. The isopropyl acetate layer was dried over $MgSO_4$, filtered, and concentrated to a brown oil. The oil was dissolved in 5.0 mL of isopropanol and 390 mg (1.3 mmol) of epoxide **P** (Example 15, part a) were added. The solution was heated to 70 °C. After 36 h, the solution was concentrated and the product purified by reversed phase HPLC (gradient of 20-70% acetonitrile in 0.1% TFA). Fractions containing pure product were combined and concentrated to remove acetonitrile. The aqueous residue was diluted with brine and extracted with ethyl acetate. The ethyl acetate layer was dried over $MgSO_4$ and concentrated to afford compound **Q** as a yellow foam.

Example 39: Synthesis of compound 39



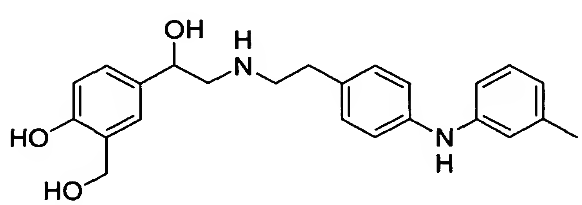
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3,4-dimethylaniline (available from Aldrich), a TFA salt of compound **39** was prepared.

Example 40: Synthesis of compound 40



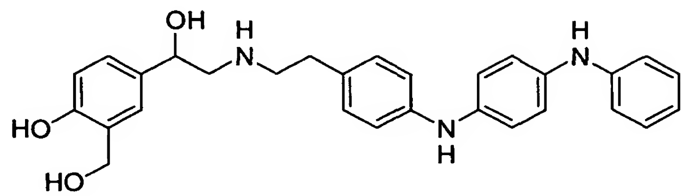
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 5-aminoindan (available from Aldrich), a TFA salt of compound **40** was prepared.

Example 41: Synthesis of compound 41



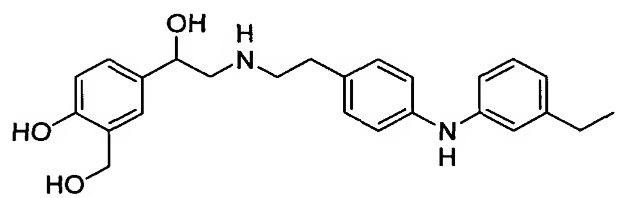
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with m-toluidine (available from Aldrich), a TFA salt of compound **41** was prepared.

Example 42: Synthesis of compound 42



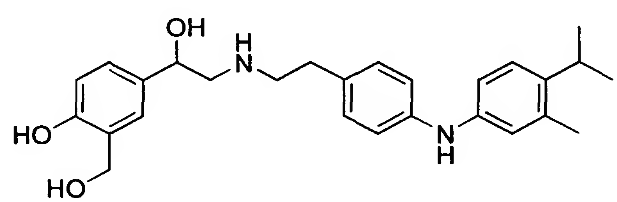
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-aminodiphenylamine (available from Aldrich), a TFA salt of compound **42** was prepared.

Example 43: Synthesis of compound 43



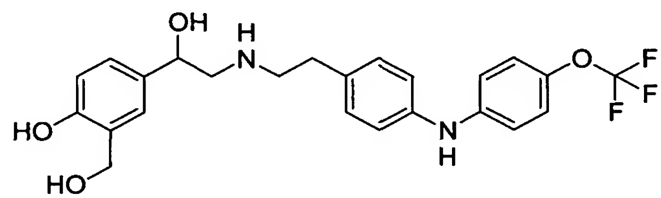
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-ethylaniline (available from Aldrich), a TFA salt of compound **43** was prepared. *m/z*: [M + H^+] calcd for $C_{25}H_{30}N_2O_3$ 407.2; found 407.2.

Example 44: Synthesis of compound 44



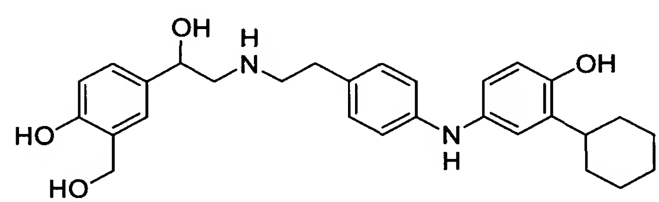
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-methyl-4-isopropylaniline hydrochloride (available from Avocado Chemicals), a TFA salt of compound **44** was prepared. *m/z*: [M + H^+] calcd for $C_{27}H_{34}N_2O_3$ 435.3; found 435.2.

Example 45: Synthesis of compound 45



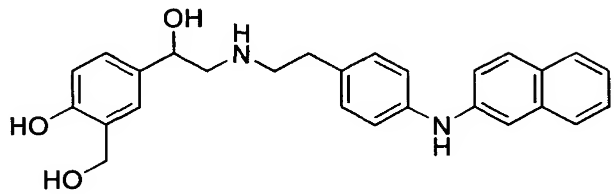
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-(trifluoromethoxy)aniline (available from Aldrich), a TFA salt of compound **45** was prepared. *m/z*: [M + H^+] calcd for $C_{24}H_{25}F_3N_2O_4$ 463.2; found 463.2.

Example 46: Synthesis of compound 46



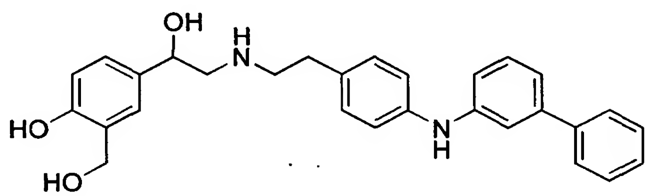
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-amino-2-cyclohexylphenol (available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **46** was prepared. *m/z*: [M + H^+] calcd for $C_{29}H_{36}N_2O_4$ 477.3; found 477.2.

Example 47: Synthesis of compound 47



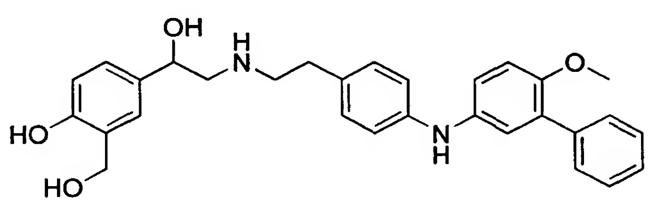
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 2-naphthylamine (available from Aldrich), a TFA salt of compound **47** was prepared.

Example 48: Synthesis of N-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (48)



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-aminobiphenyl (available from Trans World Chemicals, Inc.), a TFA salt of compound **48** was prepared.

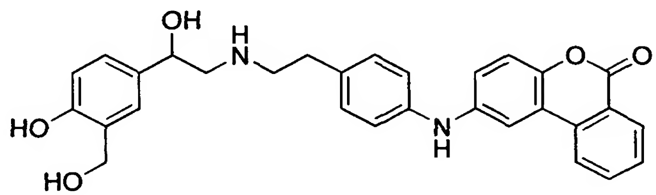
Example 49: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (49)



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 3-phenyl-p-

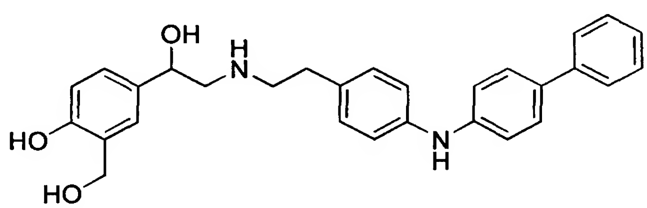
anisidine hydrochloride (available from Trans World Chemicals, Inc.), a TFA salt of compound **49** was prepared.

Example 50: Synthesis of compound 50



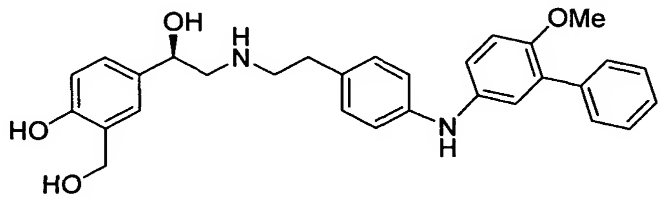
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 6-amino-3,4-benzocoumarin (available from Aldrich), a TFA salt of compound **50** was prepared. *m/z*: [M + H$^+$] calcd for $C_{30}H_{28}N_2O_5$ 497.2; found 497.1.

Example 51: Synthesis of compound 51



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with 4-aminobiphenyl (available from Aldrich), a TFA salt of compound **51** was prepared. *m/z*: [M + H$^+$] calcd for $C_{29}H_{30}N_2O_3$ 455.2; found 455.2.

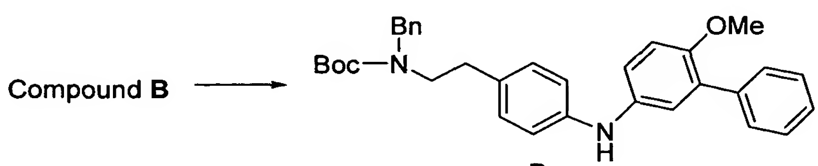
Example 52: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (52)



To 2.0 g (3.10 mmol) of compound **H** in 50mL of ethanol was added 0.70 g of 10% palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 1.5 hours. The reaction was filtered through celite, using methanol to rinse, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 mL isopropanol, 1.65 mL of 4.0 N HCl in dioxane was added, and the product was precipitated by adding the solution to a large volume of diethyl ether. The solids were isolated by filtration to give 1.43 g (80%) of a hydrochloride salt of compound **52** as a white solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.4 (b, 1H), 9.01 (br s, 1H), 8.65 (br s, 1H), 7.39-7.22 (m, 6H), 6.99-6.83 (m, 8H), 6.69 (d, 1H), 5.45 (br, 4H), 4.77 (m, 1H), 4.39 (s, 2H), 3.62 (s, 3H), 3.02-2.78 (m, 6H). *m/z*: [M + H$^+$] calcd for $C_{30}H_{32}N_2O_4$ 485.2; found 485.4.

The intermediate compound **H** was prepared as follows.

a. Synthesis of compound **D**.

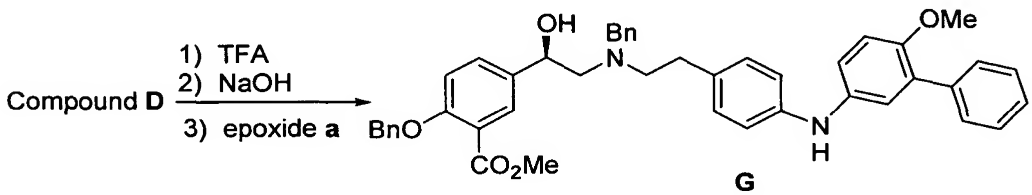


D

To a flask containing 3.91 g (10 mmol) of compound **B** (Example 13, part b), 3.06 g (13mmol) of 4-methoxy-3-phenylaniline hydrochloride (from TCI), 0.46 g (0. 5mmol) of tris(dibenzylidineacetone)dipalladium(0), 0.93 g (1.5 mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 2.21 g (23 mmol) of sodium *tert*-butoxide

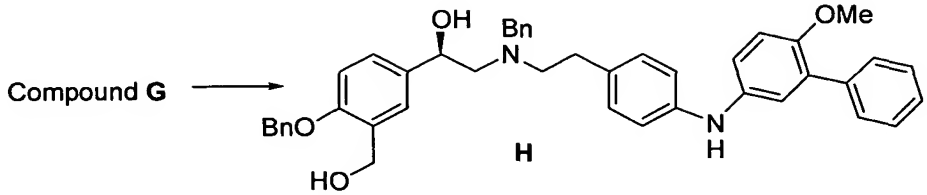
was added 50mL of toluene, and the mixture was heated at 95°C for 5.5 hours under an nitrogen atmosphere. The mixture was partitioned between 1.0 M aqueous $NaHSO_4$ and diethyl ether, and the phases were separated. The diethyl ether phase was diluted with one volume of hexanes, and was washed once each with 1.0 M aqueous $NaHSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography, using 12% EtOAc / 88% hexanes as eluent, to give compound **D** as a yellow foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.76 (s, 1H), 7.38-7.13 (m, 10H), 6.95-6.81 (m, 7H), 4.28 (s, 2H), 3.61 (s, 3H), 3.16 (m, 2H), 2.53 (m, 2H), 1.29 (s, 9H).

b. Synthesis of compound **G**.



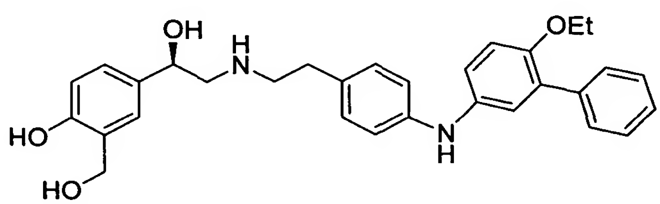
To 2.60 g (5.11mmol) of compound **D** in 15 mL of CH_2Cl_2 at 0°C was added 15 mL of trifluoroacetic acid. After 40 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between 1M aqueous NaOH and EtOAc. The phases were separated, and the EtOAc phase was washed once each with water and brine, dried over Na_2SO_4, filtered, and concentrated to an orange residue. The residue was dissolved in 15mL of isopropanol, 1.45 g (5.11 mmol) of the epoxide **a** (Example 37, part b) was added, and the solution was heated at 78°C overnight. The mixture was cooled to room temperature, and concentrated under reduced pressure to give compound **G** as an orange oil which was used in the next step without purification.

c. Synthesis of compound **H**.



To 5.11 mmol of crude compound **G** from the previous step in 40 mL of tetrahydrofuran at 0°C was added 12.7 mL (12.7 mmol) of 1.0 M lithium aluminum hydride in tetrahydrofuran. After 2 hours, the reaction was quenched by slow addition of sodium sulfate decahydrate. The slurry was diluted with diethyl ether, dried over Na_2SO_4, filtered, and concentrated to an orange oil. The oil was purified by chromatography, using 50% EtOAc / 50% hexanes as eluent, to give 2.0 g (61%, 2 steps) of compound **H** as a white foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.72 (s, 1H), 7.38-6.77 (m, 25H), 5.00 (s, 2H), 4.92 (m, 1H), 4.65 (m, 1H), 4.55 (m, 1H), 4.45 (d, 2H), 3.62 (s, 2H), 3.61 (s, 3H), 2.52 (m, 6H).

Example 53: Synthesis of *N*-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-hydroxymethyl-4-hydroxyphenyl)ethylamine (53)

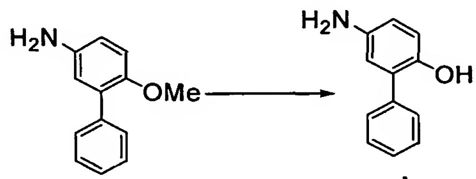


To a mixture of 825 mg (1.22 mmol) of compound **N** in 15 mL of ethanol was added 260 mg of 10% palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 3 hours. The reaction was filtered through celite, using methanol to rinse, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 10 mL isopropanol, 0.67 mL of 4.0 M HCl in dioxane was added, and the product was precipitated by adding the solution to a large volume of EtOAc. The solids were isolated by filtration to give a

hydrochloride salt of compound **53** as a white solid. *m/z*: [M + H$^+$] calcd for $C_{31}H_{32}N_2O_4$ 499.3; found 499.3.

The intermediate compound **N** was prepared as follows.

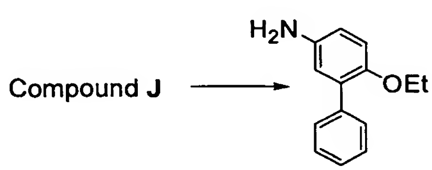
a. Synthesis of compound **J**.



J

4.84 g (20.5 mmol) of 4-methoxy-3-phenylaniline hydrochloride (available from TCI) was partitioned between diethyl ether and 1.0 M aqueous NaOH, and the phases were separated. The diethyl ether phase was washed once each with water and brine, dried over K_2CO_3, filtered, and concentrated to a brown solid. The solid was dissolved in 100 mL of CH_2Cl_2, the solution was cooled to 0°C, and 21.2 g (84.6 mmol) of boron tribromide was added. After 20 minutes, the reaction was poured over 500 mL of ice, and the mixture was stirred overnight. The mixture was washed twice with EtOAc to remove oxidized material, and the EtOAc phases were discarded. The acidic phase was basified with solid $NaHCO_3$, and was extracted twice with EtOAc. The combined EtOAc phases were washed once with brine, dried over Na_2SO_4, filtered, and concentrated to give 2.48 g of compound **J** as a brown solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.37 (s, 1H), 7.41-7.14 (m, 5H), 6.57-6.32 (m, 3H), 4.45 (s, 2H).

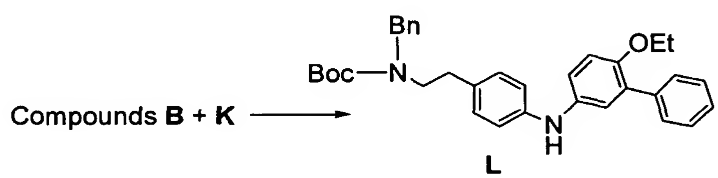
b. Synthesis of compound **K**.



K

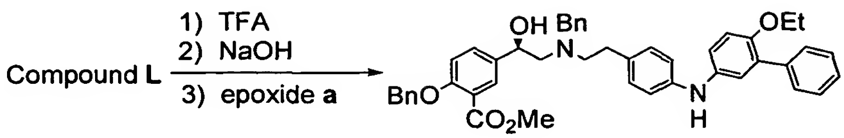
To 2.28 g (12.2 mmol) of compound **J** in 45 mL of dimethylformamide at 0°C was added 734 mg (18.4mmol) of 60% NaH in oil. After 10 minutes, 1.90 g (12.2 mmol) of iodoethane was added. After 20 minutes, the solution was partitioned between diethyl ether and 5% aqueous Na_2SO_3, and the phases were separated. The diethyl ether phase was washed once each with 1.0 M aqueous NaOH, water, and brine, dried over Na_2SO_4, and concentrated to give compound **K** as a dark brown oil. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.37-7.19 (m, 5H), 6.73 (d, 1H), 6.47-6.42 (m, 2H), 4.65 (s, 2H), 3.73 (q, 2H), 1.07 (t, 3H).

c. Synthesis of compound **L**.



To a flask containing 3.97 g (10.7 mmol) of compound **B** (Example 13, part b), 2.27 g (12.2 mmol) of compound **K**, 0.46 g (0.5 mmol) of tris(dibenzylidineacetone)dipalladium (0), 0.95 g (1.5mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 1.27 g (13.3 mmol) of sodium *tert*-butoxide was added 48 mL of toluene, and the mixture was heated at 95°C for 5.5 hours under an nitrogen atmosphere. The mixture was partitioned between 1.0 M aqueous $NaHSO_4$ and diethyl ether, and the phases were separated. The diethyl ether phase was diluted with one volume of hexanes, and was washed once each with 1.0 M aqueous $NaHSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography, using 10% EtOAc / 90% hexanes as eluent, to give 4.13 g (77%) of compound **L** as a yellow foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 7.76 (s, 1H), 7.42-7.13 (m, 10H), 6.93-6.81 (m, 7H), 4.27 (s, 2H), 3.86 (q, 2H), 3.25 (m, 2H), 2.53 (m, 2H), 1.28 (s, 9H), 1.13 (t, 3H).

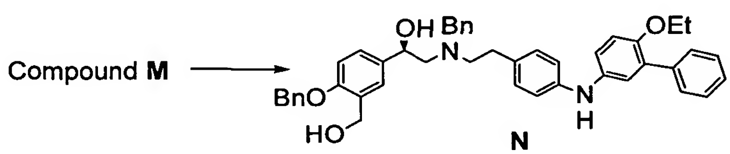
d. Synthesis of compound **M**.



M

To 1.40 g (2.68 mmol) of compound **L** in 15 mL of CH_2Cl_2 at 0°C was added 15 mL of trifluoroacetic acid. After 40 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between 1.0 M aqueous NaOH and EtOAc. The phases were separated, and the EtOAc phase was washed once each with water and brine, dried over Na_2SO_4, filtered, and concentrated to an orange residue. The residue was dissolved in 15 mL of isopropanol, 1.45 g (2.68 mmol) of the epoxide **a** (Example 37, part b) was added, and the solution was heated at 78°C overnight. The mixture was cooled to room temperature, and concentrated under reduced pressure to give an orange oil that was taken on without analysis.

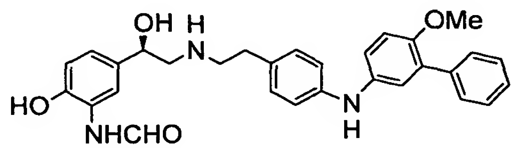
e. Synthesis of compound **N**.



N

To 2.68 mmol of crude compound **M** in 20 mL of tetrahydrofuran at 0°C was added 7.0 mL (7.0mmol) of 1.0 M lithium aluminum hydride in tetrahydrofuran. After 2 hours, the reaction was quenched by slow addition of sodium sulfate decahydrate. The slurry was diluted with diethyl ether, dried over Na_2SO_4, filtered, and concentrated to an orange oil. The oil was purified by silica gel chromatography, using 50% EtOAc / 50% hexanes as eluent, to give 835 mg of compound **N** as a white foam. ^1H NMR (300 MHz, DMSO-*d6*) δ 7.73 (s, 1H), 7.42-6.77 (m, 25H), 5.00 (s, 2H), 4.93 (m, 1H), 4.66 (d, 1H), 4.51 (m, 1H), 4.47 (m, 2H), 3.86 (q, 2H), 3.62 (m, 2H), 2.55 (m, 6H), 1.13 (t, 3H).

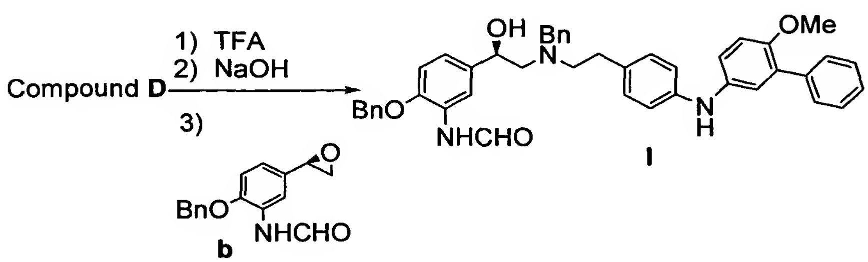
Example 54: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine (54)



To a mixture of 1.24 g (1.83 mmol) of compound **I** in 30 mL of ethanol and 20 mL of methanol was added 400mg of 10% palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 1.5 hours. The reaction was filtered through celite, using methanol to rinse, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 mL isopropanol, 0.21 mL of 4.0 M HCl in dioxane was added, and the product was precipitated by adding the solution to a large volume of EtOAc. The solids were isolated by filtration to give 447 mg of a hydrochloride salt of compound **54** as a white solid. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.03 (br s, 1H), 9.55 (s, 1H), 8.81 (br s, 1H), 8.59 (br s, 1H), 8.20 (d, 1H), 8.07 (d, 1H), 7.39-7.20 (m, 5H), 6.99-6.79 (m, 10H), 4.75 (m, 1H), 3.62 (s, 3H), 3.03-2.72 (m, 6H). *m/z*: [M + H$^+$] calcd for $C_{30}H_{31}N_3O_4$ 498.2; found 498.5.

The intermediate compound **I** was prepared as follows.

a. Synthesis of compound **I**.

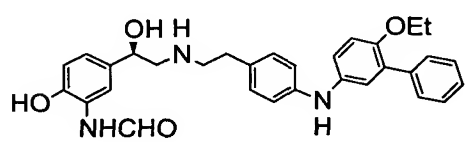


To 944 mg (1.85 mmol) of compound **D** (Example 52, part a) in 6 mL of CH_2Cl_2 at 0°C was added 6 mL of trifluoroacetic acid. After 40 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between 1.0 M aqueous NaOH and EtOAc. The phases were separated, and the EtOAc phase was washed once each with water and brine, dried over Na_2SO_4, filtered, and concentrated to an orange oil.

The residue from above was dissolved in 5 mL of isopropanol, 500 mg (1.85 mmol) of the epoxide **b** was added, and the solution was heated at 78°C overnight. The mixture was cooled to room temperature, and concentrated under reduced pressure to give an orange oil. The oil was purified by silica gel chromatography, using 50 EtOAc / 50 hexanes as eluent, to give 825 mg (66%) of compound **I** as a white foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.45 (s, 1H), 8.24 (d, 1H), 8.09 (d, 1H), 7.72 (s, 1H), 7.42-6.77 (m, 25H), 5.09 (s, 2H), 4.49 (m, 1H), 3.67 (m, 2H), 3.61 (s, 3H), 2.50 (m, 6H).

The intermediate epoxide **b** can be prepared as described in U.S. Patent No. 6,268,533 B1, and in R. Hett. et al., *Organic Process Research and Development,* **1998**, *2*, 96-99.

Example 55: Synthesis of *N*-{2-[4-(3-phenyl-4-ethoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine (55)

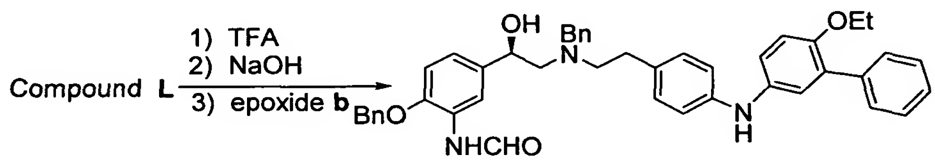


To a mixture of 746 mg (1.07 mmol) of compound **O** in 15 mL of ethanol and 5 mL of EtOAc was added 260mg of 10% palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 3 hours. The reaction was filtered through celite, using methanol to rinse, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 20 mL isopropanol, 0.58 mL of 4.0 M HCl in dioxane was added, and the product was precipitated by adding the solution to a large volume of EtOAc. The solids were isolated by filtration to give a hydrochloride salt of compound **55** as an off white solid. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.12 (br s, 1H), 9.62 (s, 1H), 8.90 (br s, 1H), 8.67 (br s, 1H),

8.27 (d, 1H), 8.14 (d, 1H), 7.25 (m, 5H) 6.85-7.08 (m, 9H), 4.80 (dd, 1H), 3.94 (quar, 2H), 2.75-3.15 (m, 6H), 1.21 (t, 3H); *m/z*: [M + H^+] calcd for $C_{31}H_{33}N_3O_4$ 512.25; found 512.5.

The intermediate compound **O** was prepared as follows.

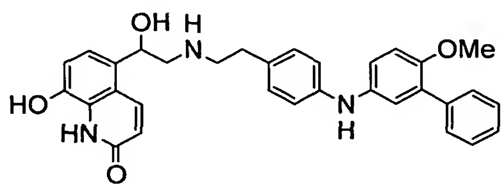
a. Synthesis of compound **O**.



O

To 1.4 g (2.68 mmol) of compound **L** (Example 53, part c) in 6 mL of CH_2Cl_2 at 0°C was added 6 mL of trifluoroacetic acid. After 40 minutes, the solution was concentrated under reduced pressure, and the residue was partitioned between 1.0 M aqueous NaOH and EtOAc. The phases were separated, and the EtOAc phase was washed once each with water and brine, dried over Na_2SO_4, filtered, and concentrated to an orange residue. The residue was dissolved in 5 mL of isopropanol, 721 mg (2.68 mmol) of epoxide **b** (Example 54, part a) was added, and the solution was heated at 78°C overnight. The mixture was cooled to room temperature, and concentrated under reduced pressure to give an orange oil. The oil was purified by silica gel chromatography using 50 EtOAc / 50 hexanes as eluent, to give 756 mg of compound **O** as a white foam. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.45 (d, 1H), 8.25 (d, 1H), 8.14 (d, 1H), 7.72 (s, 1H), 7.45-6.76 (m, 25H), 5.10 (s, 2H), 5.04 (m, 1H), 3.94 (q, 2H), 3.61 (s, 2H), 2.50 (s, 6H), 1.13 (t, 3H).

Example 56: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (56)

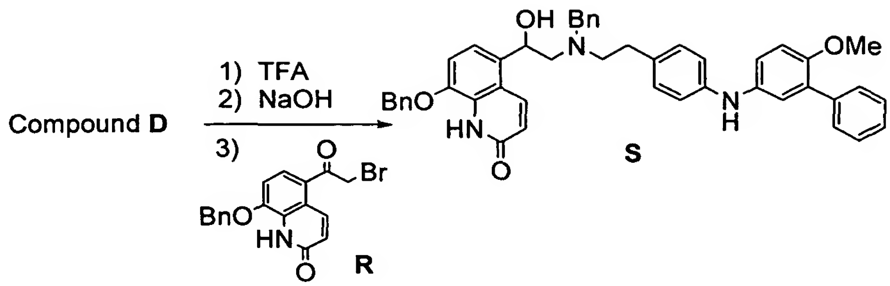


To a solution of 840 mg of compound **S** (1.2 mmol) in 40 mL of 1:1 methanol:THF was added 170 mg of 10% palladium on carbon. The reaction was shaken under an atmosphere of 35 psi H_2. After 24 h, the reaction was filtered and the filtrate purified by reversed-phase HPLC (gradient of 10 to 70% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **56** as a powder.

A sample of the TFA salt (75 mg) was dissolved in acetonitrile (1.0 mL) and diluted with water (2.0 mL) followed by 0.1 N HCl (3.0 mL). The solution became cloudy. Addition of 1.5 mL acetonitrile afforded a clear solution which was frozen and lyophilized. The residue was redissolved in acetonitrile (1.0 mL) and diluted with water (2.0 mL) followed by 0.1 N HCl (4.0 mL). The solution became cloudy. Addition of 1.0 mL acetonitrile afforded a clear solution which was frozen and lyophilized. The hydrochloride salt of compound **56** (50 mg) was obtained as a gray solid. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.55 (br s, 1H), 9.30 (br s, 1H), 8.80, (br s, 1H), 8.24 (d, 1H), 7.25-7.48 (m, 5H), 6.92-7.18 (m 9H), 6.55 (d, 1H), 5.55 (d, 1H), 3.69 (s, 3H) 2.80-3.20 (m, 6H) *m/z*: [M + H$^+$] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.3.

The intermediate compound **S** was prepared as follows.

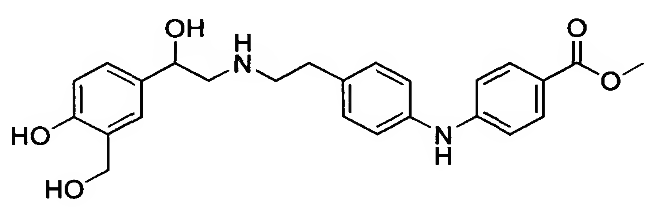
a. Synthesis of compound **S.**



A solution of compound **D** (800 mg, 1.6 mmol, Example 52, part a) in 5 mL CH_2Cl_2 was cooled to 0 °C and 5 mL of TFA was added. After 20 min, the reaction was concentrated and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed twice with 1.0 M aqueous NaOH followed by water and then dried over $MgSO_4$, filtered and concentrated to an oil. The oil was dissolved in 3 mL DMF and bromoketone **R** (800 mg, 2.1 mmol) and K_2CO_3 (650 mg, 4.7 mmol) were added. The reaction was heated to 40°C. After 1 h, the reaction was cooled and diluted with 5 mL methanol. $NaBH_4$ (150 mg, 4.0 mmol) was added and the reaction was stirred vigorously for 10 min. The reaction was quenched by dripping the suspension into 100 mL of rapidly stirred saturated aqueous NH_4Cl. Compound **S** precipitated and was isolated by filtration, washed with water and dried.

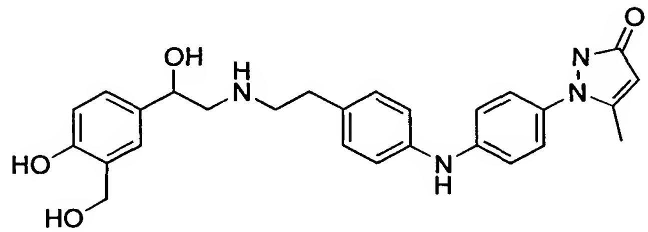
The intermediate bromoketone **R** can be prepared as described in Example 61B, parts a-d. See also EP 0 147 791 B.

Example 57: Synthesis of compound 57



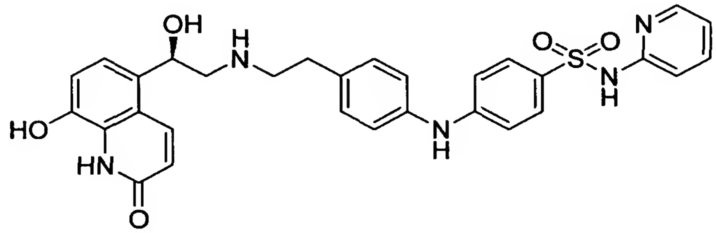
Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanilamide with methyl-4-aminobenzoate (available from Aldrich), a TFA salt of compound **57** was prepared. *m/z*: [M + H$^+$] calcd for $C_{25}H_{28}N_2O_5$ 437.2; found 437.2.

Example 58: Synthesis of compound 58



Using a coupling procedure similar to that described in Example 1, except replacing the N^1-(4-heptyl-6-methyl-2-pyrimidinyl)sulfanisamide with 2-(4-aminophenyl)-3-methyl-3-pyrazolin-5-one (available from Sigma-Aldrich Library of Rare Chemicals), a TFA salt of compound **58** was prepared. *m/z*: [M + H$^+$] calcd for $C_{27}H_{30}N_4O_4$ 475.2; found 475.2.

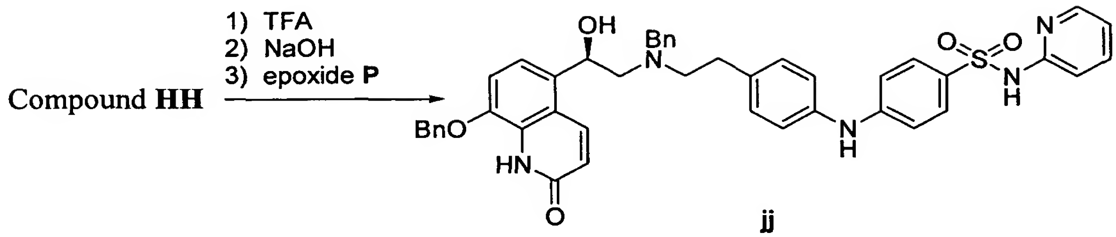
Example 59: Synthesis of compound 59



To a mixture of compound **jj** (0.2 g, 0.27 mmol) in 6 mL DMF/EtOH (1:1) was added 50 mg of 10% palladium on carbon. The reaction was agitated under H_2 at 40 psi for 8 hours. The slurry was filtered and purified by reversed phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford compound **59** as a TFA salt. The TFA salt product was solubilized in acetonitrile/water (1:1, 2 mL) to which 1.5 mL of 0.1 N aqueous HCl was added. The solution was frozen and lyophilized to afford compound **59** as an HCl salt. *m/z*: [M+H$^+$] calcd for $C_{30}H_{29}N_5O_5S$ 572.7; found 572.3.

The intermediate **jj** was prepared as follows.

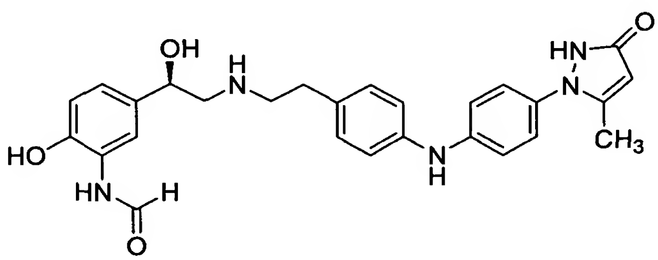
a. Synthesis of compound **jj**



jj

To compound **HH** (4.5 g, 8.1 mmol) (Example 14, part a), in 20 ml CH_2Cl_2 was added 1.5 mL TFA. After 1 hour, the solution was concentrated, basified with 1.0 N aqueous sodium hydroxide and extracted twice with CH_2Cl_2, followed by an extraction using ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to an oil. The oil was purified by silica gel chromatography (gradient of 2 to 10% methanol in methylene chloride). To the purified product (0.42 g, 0.92 mmol) was added epoxide **P** (Example 15, part a) (022 g, 0.76 mmol) and isopropanol (410 mL). The slurry was stirred at 70°C. Methylene chloride was added until a homogenous solution was obtained. After 40 h, the reaction was cooled to room temperature and the solvents were evaporated under reduced pressure. The residue was purified by silica gel chromatography (2% methanol in methylene chloride) to afford compound **jj**.

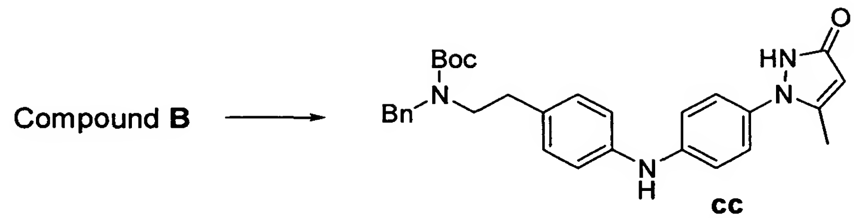
Example 60: Synthesis of compound 60



To a mixture of compound **pp** (0.3 g, 0.45 mmol) in 10 mL anhydrous EtOH was added 100 mg of 10% palladium on carbon. The reaction was agitated under H_2 at 40 psi for 18 h. The reaction was filtered and purified by reversed phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford compound **60** as a TFA salt. The TFA salt product was solubilized in acetonitrile/water (1:2, 100 mL) to which 6 mL of 0.1 N aqueous HCl was added. The solution was frozen and lyophilized to afford compound **60** as an HCl salt. *m/z*: $[M+H^+]$ calcd for $C_{27}H_{29}N_5O_4$ 488.6; found 488.3.

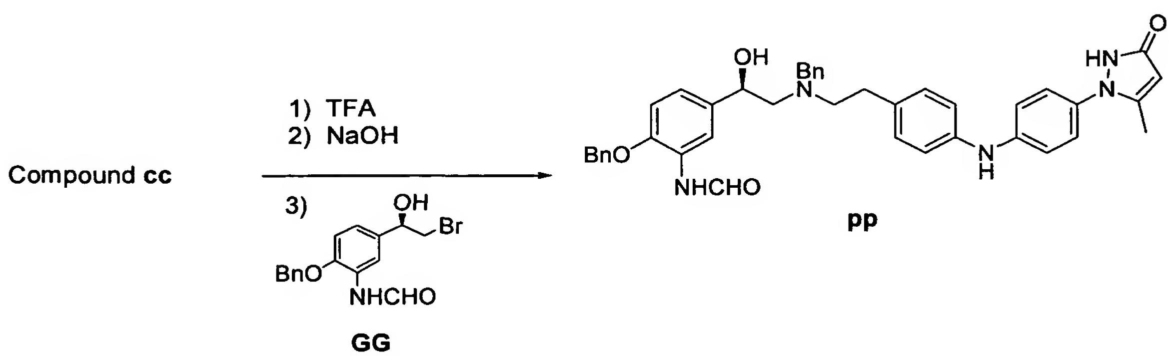
The intermediate compound **pp** was prepared as follows.

a. Synthesis of compound **cc**



To a flask containing compound **B** (Example 13, part b) (3.75 g, 9.6 mmol), 2-(4-aminophenyl)-3-methyl-3-pyrazolin-5-one (2.0 g, 10.6 mmol) (available from Sigma-Aldrich Library of Rare Chemicals), tris(dibenzylidineacetone)dipalladium(0) (0.44 g, 0.48mmol), racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.90 g, 1.44 mmol), and sodium *tert*-butoxide (2.20 g, 12.5 mmol) was added toluene (50 mL). The mixture was stirred at 95°C for 6 h under a nitrogen atmosphere. The mixture was diluted with 200 mL diethyl ether and washed twice with 100 mL portions of 1.0 M aqueous $NaHSO_4$, followed by 100 mL of saturated aqueous $NaHCO_3$. The diethyl ether phase was dried over $MgSO_4$, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography (gradient of 30 to 40% ethyl acetate in hexanes) to afford compound **cc** as an orange foam.

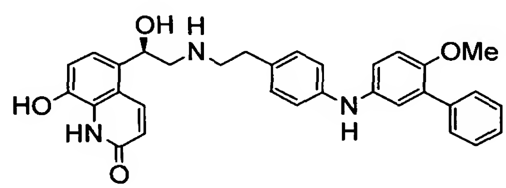
b. Synthesis of compound **pp**.



To compound **cc** (0.99 g, 1.99 mmol) in 5 mL CH_2Cl_2 was added 2 mL TFA. After 1 h, the solution was concentrated, diluted with 15 mL CH_2Cl_2 and washed with 1.0 N aqueous sodium hydroxide. The aqueous was collected and washed again with CH_2Cl_2 (10 mL) followed by a wash with ethyl acetate (10 mL). The organic layers were

combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient of 2-10% MeOH in CH_2Cl_2) to afford an oil (2.1 g). A portion of this product (0.5 g, 1.26 mmol) was solubilized in 10 mL of 1:1 methanol:THF. Bromohydrin **GG** (Example 13, part d) (0.42 g, 1.20 mmol) and K_2CO_3 (0.44 g, 3.15 mmol) were added and the slurry was stirred at room temperature for 1.5 h. The reaction was concentrated and the residue was diluted with 30 mL water and extracted twice with 30 mL portions of toluene. The toluene extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was heated to 120°C. After 2 h, the reaction was cooled to room temperature and the crude compound was purified by silica gel chromatography (gradient of 5-10% MeOH in CH_2Cl_2) to afford compound **pp** as a tan colored solid (0.7 g).

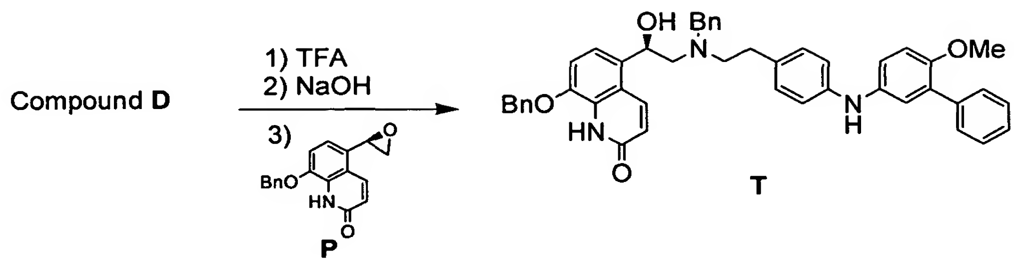
Example 61A: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (61)



To a solution of 200 mg of compound **T** (0.28 mmol) in 4 mL of acetic acid was added 100 mg of 10% palladium on carbon. The reaction was shaken under an atmosphere of 40 psi H_2. After 17 h, the reaction was filtered and the filtrate purified by reversed-phase HPLC (gradient of 10 to 70% acetonitrile in 0.1% aqueous TFA). Fractions containing pure product were combined and lyophilized to afford compound **61** as a powder.

The intermediate compound **T** was prepared as follows:

a. Synthesis of compound **T**



To 1.13 g of compound **D** (2.2 mmol, Example 52, part a) in 4 mL CH_2Cl_2 was added 4 mL TFA. After 30 minutes, the solution was concentrated and diluted with 20 mL ethyl acetate and 20 mL water. The pH was raised to 11 by addition of 6.0 N aqueous sodium hydroxide and the layers were separated. The ethyl acetate layer was washed once with 1.0 N aqueous sodium hydroxide, dried over $MgSO_4$, filtered, and concentrated to a brown oil. The oil was dissolved in 7.0 mL of isopropanol and 600 mg (2.0 mmol) of epoxide **P** (Example 15, part a) were added. The solution was heated to 70 °C. After 34 h, the solution was concentrated and the product partially purified by silica gel chromatography (gradient of 1 to 2% methanol in CH_2Cl_2). Fractions containing product were combined and concentrated to afford **T** as a yellow oil.

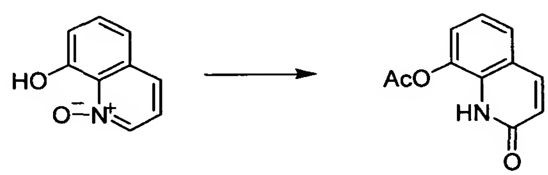
Example 61B: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (60)

To a solution of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine **(PP)** (4.0g, 6.5 mmol) in tetrahydrofuran (100 mL) and water (16 mL) was added 10% palladium on carbon (800 mg). The reaction was stirred vigorously under one atmosphere of hydrogen for 6.5 h. The solids were filtered off and washed with tetrahydrofuran (4x25 mL) and then 50% methanol/tetrahydrofuran (2x25 mL). The combined filtrates were evaporated to dryness and the crude product was purified by reverse-phase HPLC. Fractions containing pure product were combined and lyophilized. The product from several runs was combined to give 4.68 g which was dissolved in acetonitrile (200 mL) and water (200 mL). 1.0 N HCl (18.7 mL) was added, and the solution was lyophilized. The residue was again dissolved in acetonitrile (125 mL) and water (125 mL). 1.0 N HCl was added and the solution was lyophilized to give a hydrochloride salt of compound **61** as an off white powder. ^{1}H NMR

(300MHz, DMSO-*d6*) δ 10.55 (br s, 1H), 9.40 (br s, 1H), 8.80, (br s, 1H), 8.26 (d, 1H), 7.60, (br s, 2H) 7.25-7.45 (m, 5H), 6.92-7.16 (m 10H), 6.55 (d, 1H), 5.45 (d, 1H), 3.69 (s, 3H) 2.80-3.15 (m, 6H); *m/z*: [M + H^+] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.4.

The intermediate **PP** was prepared as follows:

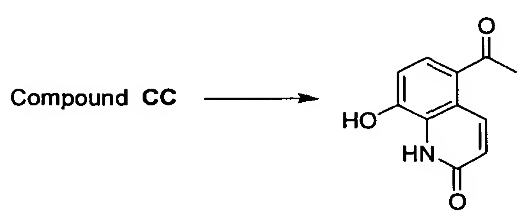
a. Synthesis of 8-acetoxy-2(1*H*)-quinolinone (**CC**)



CC

8-hydroxyquinoline-N-oxide (160.0 g, 1.0 mol) and acetic anhydride (800 mL, 8.4 mol) were heated at 100 °C for 3 hours and then cooled in ice. The product was collected on a Buchner funnel, washed with acetic anhydride (2x100mL) and dried under reduced pressure to give 8-acetoxy-2(1*H*)-quinolinone (**CC**) (144 g) as a tan solid.

b. Synthesis of 5-acetyl-8-hydroxy-2(1*H*)-quinolinone (**DD**)

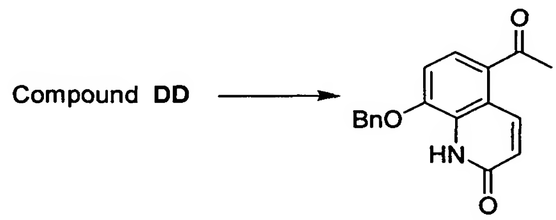


DD

A slurry of aluminum chloride (85.7 g, 640 mmol) in 1,2-dichloroethane (280 mL) was cooled in ice, and compound **CC** (56.8 g, 280 mmol) was added. The mixture was warmed to room temperature, and then heated at 85°C. After 30 minutes acetyl chloride (1.5 mL, 21 mmol) was added and the mixture was heated an additional 60 minutes. The reaction mixture was then cooled and added to 1N HCl (3 L) at 0°C with good stirring. After stirring for 2 hours, the solids were collected on a Buchner funnel, washed with water (3x250mL) and dried under reduced pressure. The crude product isolated from

several batches (135 g) was combined and triturated with dichloromethane (4 L) for 6 hours. The product was collected on a Buchner funnel and dried under reduced pressure to give 5-acetyl-8-hydroxy-2(1*H*)-quinolinone (**DD**) (121 g).

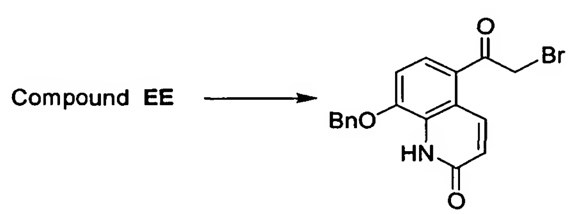
c. Synthesis of 5-acetyl-8-benzyloxy-2(1*H*)-quinolinone (**EE**)



EE

To 5-acetyl-8-hydroxy-2-quinolone (37.7 g, 186 mmol) was added dimethylformamide (200 mL) and potassium carbonate (34.5 g, 250 mmol) followed by benzyl bromide (31.8 g, 186 mmol). The mixture was stirred at room temperature for 2.25 hour and then poured into saturated sodium chloride (3.5 L) at 0°C and stirred well for 1 hour. The product was collected and dried on a Buchner funnel for 1hour, and the resulting solids were dissolved in dichloromethane (2 L) and dried over sodium sulfate. The solution was filtered through a pad of Celite and washed with dichloromethane (5x200 mL). The combined filtrate was then concentrated to dryness and the resulting solids were triturated with ether (500 mL) for 2 hours. The product was collected on a Buchner funnel, washed with ether (2x250 mL) and dried under reduced pressure to give 5-acetyl-8-benzyloxy-2(1*H*)-quinolinone (**EE**) (44 g) as an off white powder.

d. Synthesis of 5-(2-bromo-1-oxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**R**)

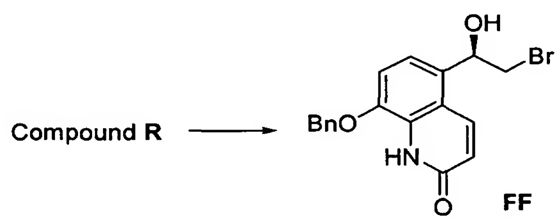


R

5-Acetyl-8-benzyloxy-2(1*H*)-quinolinone (**EE**) (20.0 g, 68.2 mmol) was dissolved in dichloromethane (200 mL) and cooled to 0°C. Boron trifluoride diethyl etherate

(10.4 mL, 82.0 mmol) was added via syringe and the mixture was warmed to room temperature to give a thick suspension. The suspension was heated at 45°C (oil bath) and a solution of bromine (11.5 g, 72.0 mmol) in dichloromethane (100 mL) was added over 40 minutes. The mixture was kept 45°C for an additional 15 minutes and then cooled to room temperature. The mixture was concentrated under reduced pressure and then triturated with 10% aqueous sodium carbonate (200 mL) for 1 hour. The solids were collected on a Buchner funnel, washed with water (4x100 mL) and dried under reduced pressure. The product of two runs was combined for purification. The crude product (52 g) was triturated with 50% methanol in chloroform (500 mL) for 1 hour. The product was collected on a Buchner funnel and washed with 50% methanol in chloroform (2x50 mL) and methanol (2x50 mL). The solid was dried under reduced pressure to give 5-(2-bromo-1-oxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**R**) (34.1 g) as an off white powder.

e. Synthesis of 5-(2-bromo-(*R*)-1-hydroxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**FF**)



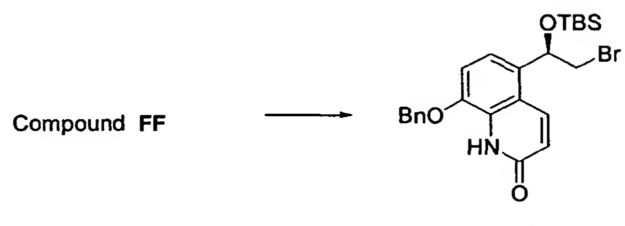
FF

Using a procedure described in Mathre et al., *J. Org. Chem.*, **1991**, *56*, 751-762, a catalyst was prepared as follows. (R)-(+)-α, α -Diphenylprolinol (10.0 g, 39 mmol) and trimethylboroxine (3.7 mL, 26 mmol) were combined in toluene (200 mL) and stirred at room temperature for 30 min. The mixture was placed in a 150°C oil bath and 150 mL liquid was distilled away. Toluene (50 mL) was added, and another 50 mL of distillate was collected. Another portion of toluene (50 mL) was added and a further 50 mL of distillate was collected. A 1.00 mL aliquot of the material remaining in the pot was evaporated to dryness and weighed (241.5 mg) to determine that the concentration of catalyst was 0.87 M.

5-(2-Bromo-1-oxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**R**) (30.0 g, 81 mmol) was suspended in, tetrahydrofuran (1.2 L) under a nitrogen atmosphere and the catalyst from above (13 mL, 11 mmol) was added. The suspension was cooled to -5°C in an ice/isopropanol bath and borane (1.0 M in THF, 97 mL, 97 mmol) was added over 3 h. The reaction was stirred an additional 45 min at -5°C, then methanol (200 mL) was added

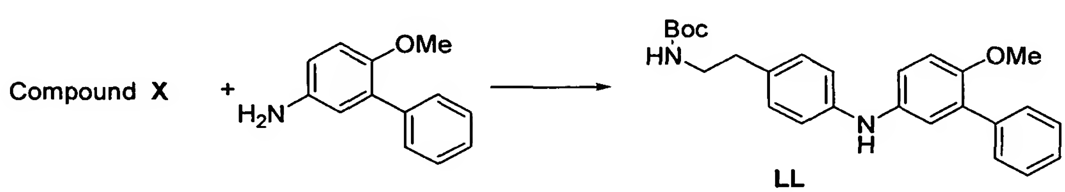
slowly. The mixture was concentrated under vacuum to give 5-(2-bromo-(*R*)-1-hydroxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**FF**).

f. Synthesis of 5-(2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**HH**)



Compound **FF** (15 g, 40 mmol) and 2,6-lutidine (9.3 mL, 80 mmol) were suspended in dichloromethane at 0°C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (18.5 mL, 80 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with dichloromethane (200 mL) and washed twice with 1N hydrochloric acid, then three times with brine. The organics were dried over magnesium sulfate and the volume was reduced to 100 mL under vacuum. The organics were applied to a silica gel column equilibrated with 30% ethyl acetate in hexanes and the product was eluted with 50% ethyl acetate in hexanes. Removal of the solvent under reduced pressure gave 5-(2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone (**HH**). (10.3 g). Unreacted starting material (compound **FF**, 2 g) was also recovered.

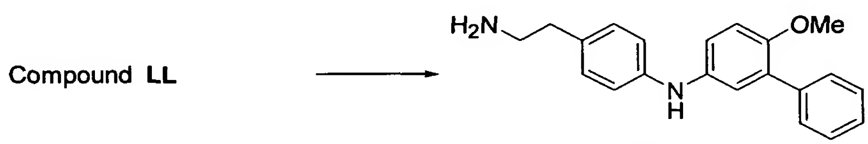
g. Synthesis of *N*-*tert*-butoxycarbonyl-2-[4-(3-[phenyl-4-methoxyphenyl)aminophenyl]ethylamine (**LL**)



Under nitrogen, compound **X** (from Example 38 part a) (5.0 g, 16.7 mmol) was mixed with toluene (80 mL) and 4-methoxy-3-phenylaniline hydrochloride (4.3 g, 18.3 mmol) was added to form a slurry. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (1.6 g,

2.5 mmol) was added, followed by tris(dibenzylideneacetone)dipalladium(0) (760 mg, 0.83 mmol) and finally sodium *tert*-butoxide (5.3 g, 55 mmol). The mixture was heated at 90°C for 150 min and then cooled to room temperature. Water (150 mL) was added followed by ethyl acetate (150 mL) and the phases partitioned. The aqueous layer was extracted with ethyl acetate (150 mL) and the combined organics washed three times with 0.5 M sodium bisulfate (200 mL), once with saturated sodium bicarbonate (150 mL) and twice with saturated sodium chloride (150 mL). The organics were dried over magnesium sulfate (50 g) and the volatiles removed under vacuum to give *N-tert*-butoxycarbonyl-2-[4-(3-[phenyl-4-methoxyphenyl)aminophenyl]ethylamine **(LL)** (8.4 g) which was used without further purification.

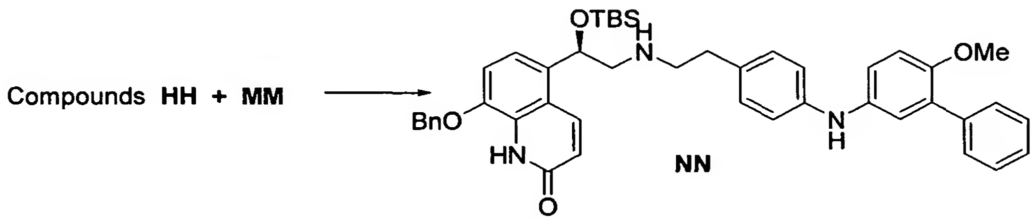
h. Synthesis of 2-[4-(3-[phenyl-4-methoxyphenyl)aminophenyl]ethylamine **(MM)**



MM

Under nitrogen, compound **LL** (94.6 g) was treated with dichloromethane (500 mL) and cooled in an ice bath. Hydrogen chloride (4 M in dioxane, 125 mL, 500mmol) was added in 10 portions over 20 min. The reaction was kept at room temperature for 130 minutes, during which time the product precipitated. The solid was filtered and washed with dichloromethane (350 mL) and dried under vacuum in the dark to give the dihydrochloride salt of 2-[4-(3-[phenyl-4-methoxyphenyl)aminophenyl]ethylamine **(MM)** (37.1 g). ^{1}H NMR (300MHz, DMSO-*d6*) δ 8.29 (br s, 2H), 8.04 (br s, 1H) 7.25-7.50 (m, 5H), 6.90-7.08 (m, 7H) 3.69 (s, 3H), 2.93 (m, 2H), 2.75 (m, 2H); *m/z*: [M + H$^+$] calcd for $C_{21}H_{22}N_2O$ 319.18; found 319.3.

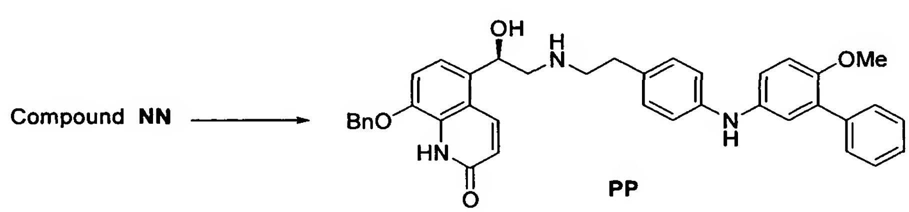
i. Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-*tert*-butyldimethylsilyl-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**NN**)



The dihydrochloride salt of compound **MM** was partitioned between isopropyl acetate and 1.0 N sodium hydroxide. The organic layer was dried over sodium sulfate and concentrated to give the free base as a dark oil.

Sodium iodide (4.2 g, 28 mmol), compound **HH** (9.1 g, 18.6 mmol) and sodium bicarbonate (4.7 g, 55.9 mmol) were weighed into a flask. Under nitrogen, compound **MM** (7 g, 22 mmol) in dimethyl sulfoxide (20 mL) was added and the mixture stirred at 140°C (oil bath) for 30 min, then cooled to room temperature. Ethyl acetate was added (200 mL) and the mixture washed three times with 1N hydrochloric acid, then with 1N sodium hydroxide, saturated sodium bicarbonate and finally saturated sodium chloride (200 mL each). The organics were dried over sodium sulfate and evaporated to dryness to give *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-*tert*-butyldimethylsilyl-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**NN**) (13.9 g) which was used in the next step without further purification.

j. Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**PP**)



Compound **NN** (13.9 g) was combined with methanol (200 mL) and concentrated hydrochloric acid (170 mL) was added in portions (exothermic). The solution turned orange and cloudy after the addition and more methanol (100 mL) was added until a clear solution was obtained. The mixture was stirred at room temperature overnight, in which

time a brown gum had formed. The solvent was removed under vacuum, and ethyl acetate (300 mL) was added. The resulting mixture was cooled in an ice bath, and neutralized (pH 7) with 10 N sodium hydroxide. The pH was then raised to 10 with 1 M sodium hydroxide to give a clear biphasic mixture. The phases were separated and the aqueous layer was extracted with ethyl acetate (300 mL). The combined organic layers were dried over sodium sulfate, and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (500 g, 0-10% methanol in dichloromethane) to give *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine **(PP)** (5.6 g).

Example 61C: Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (PP)

The intermediate compound **PP** was prepared as follows:

a. Synthesis of 5-(2-bromo-(*R*)-1-hydroxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone **(FF)**

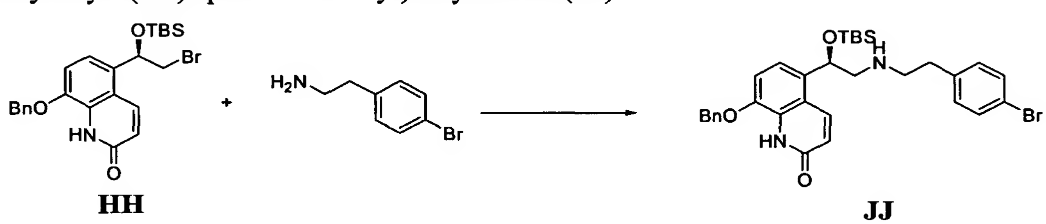
(R)-(+)-α,α-Diphenylprolinol (30.0 g, 117 mmol) and trimethylboroxine (11.1 mL, 78 mmol) were combined in toluene (300 mL) and stirred at room temperature for 30 minutes. The mixture was placed in a 150°C oil bath and liquid was distilled off. Toluene was added in 20 mL aliquots, and distillation was continued for 4 hours. A total of 300 mL toluene was added. The mixture was finally cooled to room temperature. A 500 μL aliquot was evaporated to dryness, weighed (246 mg) to determine that the concentration of catalyst was 1.8 M.

5-(2-Bromo-1-oxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone **(R)** (90.0 g, 243 mmol) was placed under nitrogen, tetrahydrofuran (900 mL) was added followed by the catalyst from above (1.8 M in toluene, 15 mL, 27 mmol). The suspension was cooled to -10±5°C in an ice/isopropanol bath. Borane (1.0 M in THF, 294 mL, 294 mmol) was added over 4 hours. The reaction was stirred an additional 45 minutes at -10°C, then methanol (250 mL) was added slowly. The mixture was concentrated under vacuum. The residue was dissolved in boiling acetonitrile (1.3 L), filtered while hot and cooled to room temperature. The crystals were filtered, washed with acetonitrile and dried under reduced pressure to give 5-(2-bromo-(*R*)-1-hydroxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone **(FF)** (72.5g, 196 mmol, 81% yield, 95% ee, 95% pure by HPLC area ratio).

b. Synthesis of 5-(2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone **(HH)**

Compound **FF** (70.2 g, 189 mmol) was treated with *N,N*-dimethylformamide (260 mL) and cooled in an ice bath under nitrogen. 2,6-Lutidine (40.3 g, 376 mmol) was added over 5 minutes followed slowly by *tert*-butyldimethylsilyl trifluoromethanesulfonate (99.8 g, 378 mmol), keeping the temperature below 20°C. The mixture was allowed to warm to room temperature for 45 minutes. Methanol (45 mL) was added to the mixture dropwise over 10 minutes and the mixture was partitioned between ethyl acetate/cyclohexane(1:1, 500 mL) and water/brine (1:1, 500mL). The organics were washed twice more with water/brine (1:1, 500 mL each). The combined organics were evaporated under reduced pressure to give a light yellow oil. Two separate portions of cyclohexane (400 mL) were added to the oil and distillation continued until a thick white slurry was formed. Cyclohexane (300 mL) was added to the slurry and the resulting white crystals were filtered, washed with cyclohexane (300 mL) and dried under reduced pressure to give 5-(2-bromo-(*R*)-1-*tert*-butyldimethylsiloxy)ethyl-8-benzyloxy-2(1*H*)-quinolinone **(HH)** (75.4 g, 151 mmol, 80% yield, 98.6 % ee).

c. Synthesis of *N*-[2-(4-bromophenyl)ethyl}-(*R*)-2-*tert*-butyldimethylsiloxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (JJ)



Compound **HH** (136.5 g, 279 mmol), 4-bromophenethylamine (123 g, 615 mmol) and dimethyl sulfoxide (180 mL) were mixed at room temperature under nitrogen. Another 40 mL of dimethyl sulfoxide was added. The mixture was heated to 85°C for 5 hours. The reaction was partitioned between ethyl acetate (1 L) and 10% aqueous acetic acid (500 mL). The organics were washed with 10% aqueous acetic acid (3x500 mL), then with 1N sodium hydroxide (3x500 mL). The last wash was filtered through Celite (100 g). The organic layer was concentrated to 300 mL and cyclohexane (2x500 mL) was added and the solution concentrated to 300 mL. Sufficient cyclohexane was added to form 1.8 L final volume which was filtered through Celite (50 g). A solution of HCl in

isopropanol, prepared by slowly adding concentrated HCl (23.5 mL) to isopropanol (180 mL) at 10°C (internal), was added to the crude product and the reaction mixture was stirred for 5 hours, washed with cyclohexane (2x500 mL) and dried under reduced pressure for 24 hours to give *N*-[2-(4-bromophenyl)ethyl}-(*R*)-2-*tert*-butyldimethylsiloxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**JJ**) hydrochloride (145 g, 80 mol %, 106 wt %, HPLC purity 97.9 %).

d. Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-*tert*-butyldimethylsilyl-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**NN**)

To compound **JJ** hydrochloride (73.7 g, 114 mmol) and 4-methoxy-3-phenylaniline hydrochloride (32.4 g, 137 mmol), toluene (380 mL) was added with mild agitation for 5 minutes, followed by sodium *tert*-butoxide (49.3 g, 513 mmol) in portions over 1 minute, and finally 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (10.65 g, 17 mmol) and tris(dibenzylideneacetone)dipalladium(0) (5.22 g, 5.7 mmol). The resulting mixture was stirred and heated to 85-89°C (internal) for 2.5 hours. The solution was cooled to room temperature, water (400 mL) was added and the mixture was stirred for 5 minutes, filtered through Celite (80 g), and partitioned with toluene (100 mL). The organic layer was collected and concentrated under reduced pressure in a 40°C bath to give *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-*tert*-butyldimethylsilyl-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**NN**) as a dark viscous oil.

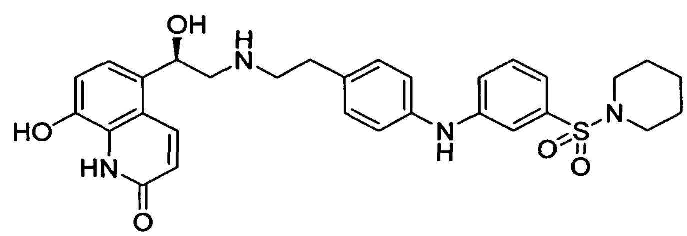
e. Synthesis of *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine (**PP**)

Compound **NN** from the previous step was dissolved in 280 ml of THF. Triethylamine trihydrofluoride (27.6 g, 171 mmol) was added to the solution, an additional 20 mL of THF was used to rinse down residual reagent, and the reaction was stirred at 25°C under nitrogen for 16 hours. The reaction mixture was concentrated under reduced pressure in a 25°C bath to give a dark viscous oil to which dichloromethane (400 mL) was added, followed by 1N aqueous NaOH (200 mL). The reaction mixture was stirred for 5 hours. The top layer was discarded and the organic layer was concentrated to a viscous oil.

The oil was dissolved in dichloromethane to give a total volume of 630 mL. A 60 mL aliquot was taken and concentrated to 30 mL. Toluene (60 mL) was added,

followed by a mixture of concentrated hydrochloric acid (2.7 mL) and methanol (4.5 mL) to give a thick paste covered in a free-flowing liquid. The liquid was carefully removed and the paste washed with toluene (50 mL). The gum was partitioned between dichloromethane (40 mL) and 1N aqueous sodium hydroxide (40 mL) and the organic solvents were removed under reduced pressure. The residue was purified chromatographically over silica using a gradient of 0-10% methanol in dichloromethane to give *N*-{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-benzyloxy-2(1*H*)-quinolinon-5-yl)ethylamine **(PP)**.

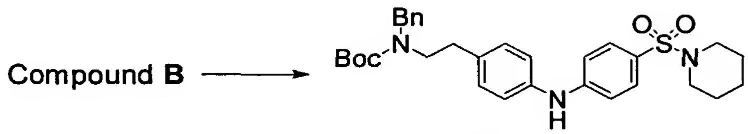
Example 62: Synthesis of compound 62



To a solution of 70 mg of compound **nn** (0.09 mmol) in 5 mL of glacial acetic acid was added 21 mg of 10% palladium on carbon. The reaction was shaken under an atmosphere of H_2 at 40 psi. After 18 h, the reaction was filtered and the filtrate purified by reversed-phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA) to afford compound **62** (10 mg, 0.0126 mmol) as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21-1.33 (m, 2H), 1.39-1.52 (m, 4H), 2.74 (m, 4H), 2.82 (m, 2H), 2.96-3.20 (m, 4H), 5.25 (m, 1H), 6.13 (m, 1H), 6.51 (m, 1H), 6.90 (d, 1H, J=8.2 Hz), 7.01 (d, 2H, J=8.8 Hz), 7.07-7.15 (m, 5H), 7.43 (d, 2H, J=9.1 Hz), 8.07 (d, 2H, J=9.9 Hz), 8.61 (br s, 2H), 8.76 (s, 1H), 10.39 (s, 1H), 10.46 (s, 1H). *m/z*: [M+H$^+$] calcd for $C_{30}H_{34}N_4O_5S$ 563.7; found 563.3.

The intermediate compound **nn** was prepared as follows.

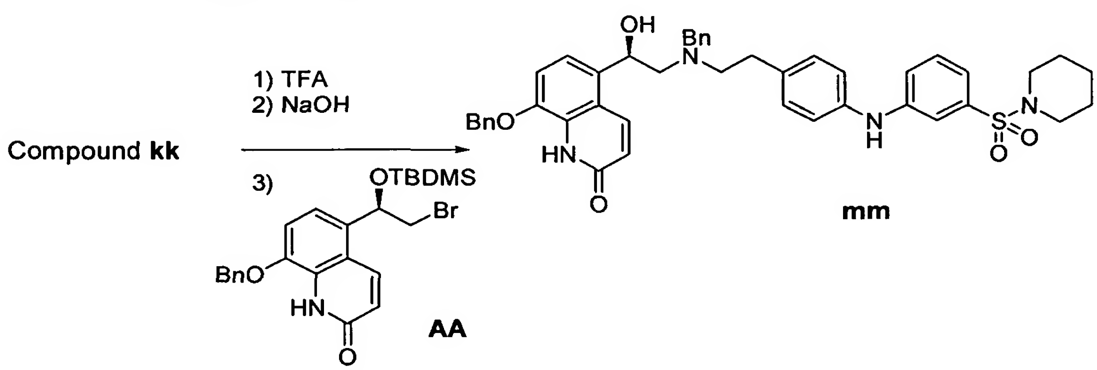
a. Synthesis of compound **kk**.



kk

To a flask containing 4.51 g (11.6 mmol) of compound **B** (Example 13, part b), 3.61 g (15.0 mmol) of 4-(piperdinosulfonyl)aniline (available from Maybridge), 0.53 g (0.58mmol) of tris(dibenzylidineacetone)dipalladium(0), 1.19 g (1.91 mmol) of racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, and 1.45 g (15.1 mmol) of sodium tert-butoxide was added toluene (60 mL), and the mixture was stirred at 95°C for 6 h under a nitrogen atmosphere. The mixture was diluted with 200 mL diethyl ether and washed twice with 100 mL portions of 1.0 M aqueous $NaHSO_4$, followed by 100 mL of saturated aqueous $NaHCO_3$. The diethyl ether phase was dried over $MgSO_4$, filtered, and concentrated to a dark oil. The oil was purified by silica gel chromatography (gradient of 30 to 40% ethyl acetate in hexanes) to afford compound **kk** as an orange foam.

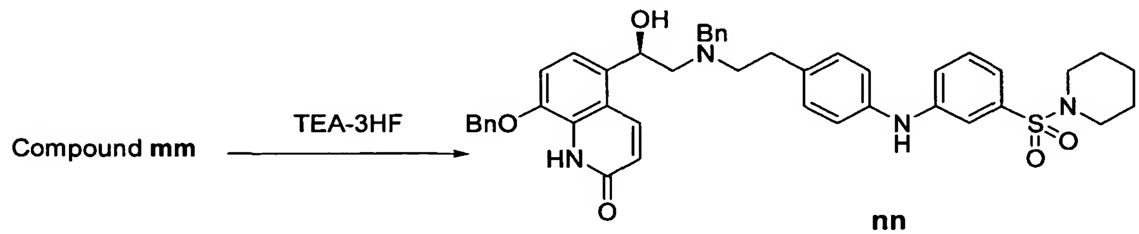
b. Synthesis of compound **mm**.



A solution of compound **kk** (2.88 g, 5.24 mmol) in 20 mL CH_2Cl_2 was cooled to 0 °C and 20 mL of TFA was added. After 20 min, the reaction was concentrated and the residue dissolved in isopropyl acetate. The isopropyl acetate solution was washed twice with 1.0 N aqueous NaOH followed by water and then dried over $MgSO_4$, filtered and concentrated to an oil. The oil was dissolved in 2 mL DMF and intermediate **AA** (337 mg, 0.69 mmol), diethyl isopropyl amine (179 mg, 1.38 mmol) and potassium iodide (172 mg, 1.04 mmol) were added. The reaction was heated to 100°C. After 18 h, the reaction was cooled and added to vigorously stirred ice water. Compound **mm**

precipitated, was isolated by filtration and purified by silica gel chromatography (1:1 ethyl acetate/hexanes) to afford 544 mg solid.

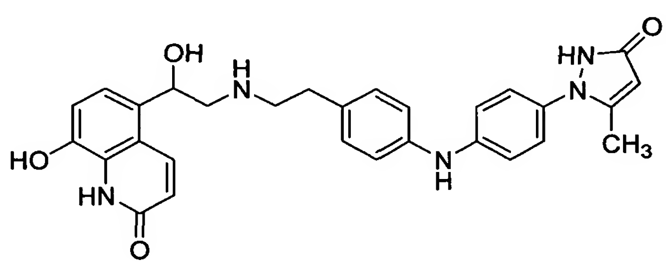
c. Synthesis of compound **nn**.



nn

To a solution of compound **mm** (83 mg, 0.01 mmol) in CH_2Cl_2 (0.9 mL) and triethylamine (0.09 mL) was added triethylamine trihydrofluoride (313 mg, 1.94 mmol). The solution was stirred at room temperature under a N_2 atmosphere. After 18 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 1.0 N aqueous HCl, followed by two washes with saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford compound **nn** (70 mg).

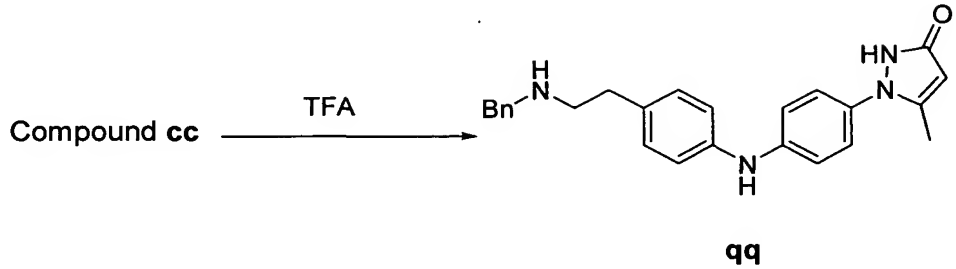
Example 63: Synthesis of compound 63



To a solution of 730 mg of compound **rr** (1.05 mmol) in 10 mL of glacial acetic acid was added 100 mg of 10% palladium on carbon. The reaction was stirred under an atmosphere of H_2. After 65 h, the reaction was filtered and the filtrate purified by reversed-phase HPLC (gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA) to afford 90 mg (0.14 mmol) the TFA salt. The TFA salt product was solubilized in acetonitrile/water (1:2, 10 mL) to which 3 mL of 0.1 N aqueous HCl was added. The solution was frozen and lyophilized to afford compound **63** as an HCl salt. *m/z*: $[M+H^+]$ calcd for $C_{29}H_{29}N_5O_4$ 512.6; found 512.3.

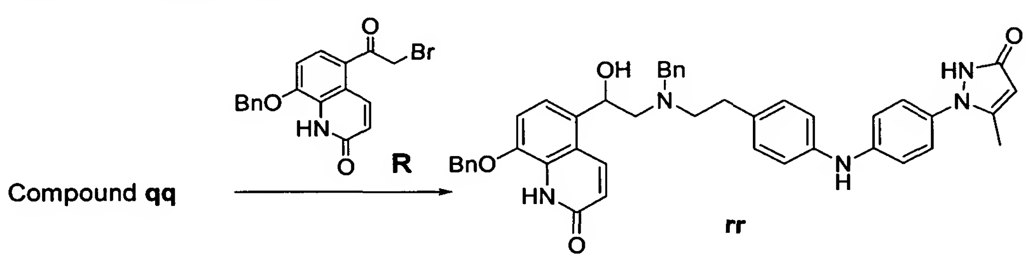
Intermediate **rr** was prepared as follows.

a. Synthesis of compound **qq**



To 0.99 g of compound **cc** (Example 60, part a) (1.99 mmol) in 5 mL CH_2Cl_2 was added 2 mL TFA. After 1 h, the solution was concentrated, diluted with 15 mL CH_2Cl_2 and washed with 1.0 N aqueous sodium hydroxide. The aqueous was collected and washed again with CH_2Cl_2 (10 mL) followed by a wash with ethyl acetate (10 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient of 2-10% MeOH in CH_2Cl_2) to afford intermediate **qq** as an oil.

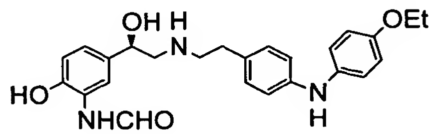
a. Synthesis of compound **rr**.



To a solution of compound **qq** (2.0 6, 5.0 mmol) in 27 mL DMF were added bromoketone **R** (from Example 56, part a) (1.71 g, 4.5 mmol) and K_2CO_3 (1.91 g, 13.8 mmol). The reaction was heated to 50°C. After 1 h, the reaction was allowed to cool to room temperature and the K_2CO_3 was filtered off. The filtrate was diluted with CH_2Cl_2 (50 mL) and was washed with 0.1N HCl (30 mL). The organic layer was washed once with saturated sodium bicarbonate solution, followed by aqueous saturated sodium chloride, dried over Na_2SO_4 and concentrated under reduced pressure to afford an oil. The product (1.14 g, 1.65 mmol) was solubilized in 12 mL THF/EtOH (1:1) and $NaBH_4$

(380 mg, 10.0 mmol) was added. After 20 minutes of vigorous stirring. The reaction was quenched with saturated aqueous NH_4Cl which was added until effervescence of the reaction mixture ceased. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed twice with saturated sodium bicarbonate, followed by saturated sodium chloride, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (2% MeOH in CH_2Cl_2) to yield 230 mg of intermediate **rr**.

Example 64: Synthesis of N-{2-[4-(4-ethoxyphenyl)aminophenyl]ethyl}-(R)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine (64)

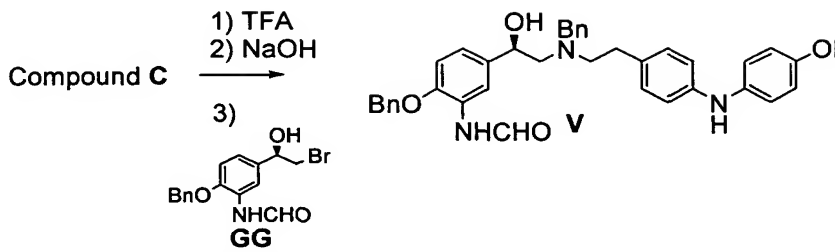


To a mixture of 580 mg (0.93 mmol) of compound **V** in 25 mL of ethanol was added 173 mg of 10% palladium on carbon under a stream of nitrogen. The flask was fitted with a balloon of hydrogen gas, and the reaction was vigorously stirred for 4 days. The reaction was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC using a gradient of 10 to 50% acetonitrile in 0.1% aqueous TFA. Fractions containing pure product were combined and lyophilized to afford a TFA salt of compound **64** as an off-white powder.

A sample of the TFA salt of compound **64** (150 mg) was dissolved in acetonitrile (2.0 mL) and water (2.0 mL). 0.1N HCl (7.0 mL, 0.70 mmol) was added, and the resulting precipitate was redissolved by the addition of acetonitrile. The resulting solution was lyophilized to give a solid which was again dissolved in acetonitrile (5.0 mL) and water (5.0 mL). 0.1N HCl (7.0mL, 0.7 mmol) was added and the resulting solution was lyophilized to give a hydrochloride salt of compound **64** as an off white powder. ^1H NMR (300MHz, DMSO-*d6*) δ 10.10 (br s, 1H), 9.62 (s, 1H), 8.80 (br s, 1H), 8.65 (br s, 1H), 8.27 (d, 1H), 8.15 (d, 1H), 6.80-7.15 (m, 11H), 4.78 (dd, 1H), 3.94 (quar, 2H), 2.80-3.15 (m, 6H), 1.29 (t, 3H); *m/z*: [M + H$^+$] calcd for $C_{25}H_{29}N_3O_4$ 436.22; found 436.3.

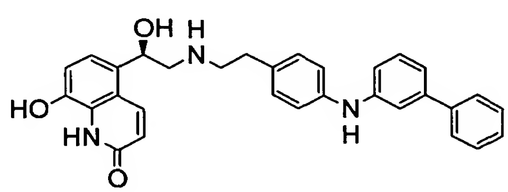
The intermediate compound **V** was prepared as follows.

a. Synthesis of compound **V**.



To 0.60 g (1.3 mmol) of compound **C** (Example 37, part a) in 20 mL of CH_2Cl_2 at 0°C was added 2.0 mL of trifluoroacetic acid. After 1 h, the solution was concentrated under reduced pressure, and the residue was partitioned between 1.0 M aqueous NaOH and EtOAc. The phases were separated, and the EtOAc phase was dried over $MgSO_4$, filtered, and concentrated to an oil and dissolved in 10 mL of 1:1 methanol:THF. Bromohydrin **GG** (Example 13, part d) (360 mg, 1.0 mmol) and K_2CO_3 (380 mg, 2.7 mmol) were added and the reaction was stirred at room temperature for 1.5 h. The reaction was diluted with 30 mL water and extracted twice with 30 mL portions of toluene. The toluene extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was heated to 120°C. After 2h, the residue was cooled to room temperature and purified by silica gel chromatography (gradient of 5 to 10% methanol in CH_2Cl_2). Fractions containing pure product were combined and concentrated to afford compound **V** as a tan solid.

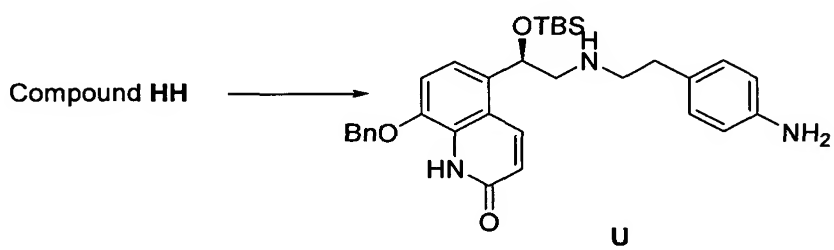
Example 65: Synthesis of *N*-{2-[4-(3-phenylphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (65)



Compound **W** (55.2 mg, 0.094 mmol), phenyl boronic acid (13.2 mg, 0.113 mmol) and [1,1'-bis(diphenylphosphinoferrocene)dichloropalladium (II), complex with dichloromethane ($PdCl_2$(dppf)-DCM) (5.0 mg, 0.006 mmol) were combined in a small pressure tube and purged with N_2. 1,2-Dimethoxyethane (1.0 mL) and 2.0 N cesium carbonate (150 μL, 0.3 mmol) were added. The tube was sealed, and then placed in an oil

bath at 90°C for 4 hours. The solution was then cooled to room temperature and DCM (10 mL) was added. The solution was filtered and concentrated to dryness. To the residue there was added DMF (1.0 mL), 10% Pd/C (100 mg) and ammonium formate (200 mg) and the solution was heated to 50°C for 1.5 hours. At this time, water:acetonitrile 1:1 and 200 μL TFA was added and the solution was filtered to remove the catalyst. The filtrate was purified by reverse phase HPLC. Fractions containing pure product were combined and lyophilized to give compound **65** as a TFA salt. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.39 (s, 1H), 8.60 (br s, 2H), 8.19 (s, 1H), 8.07 (d, 1H), 7.50 (d, 2H), 7.37 (t, 2H) 7.15-7.30 (m, 3H), 6.85-7.10 (m, 9H), 6.51 (dd, 1H), 6.11 (d, 1H), 5.23 (d, 1H), 2.70-3.15 (m, 6H); *m/z*: [M+H$^+$] calcd for $C_{31}H_{29}N_3O_3$ 492.23; found 492.3.

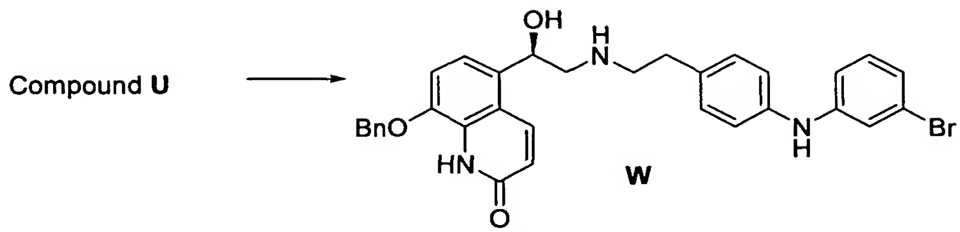
a. Synthesis of compound **U**



U

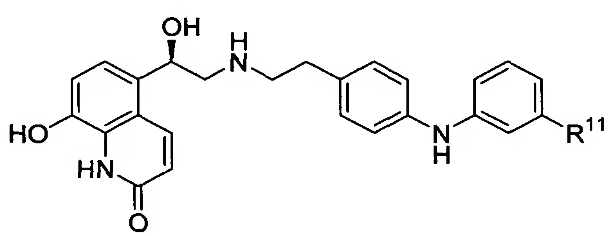
Compound **HH** (Example 61B, part f) (9.1g, 18.62mmol), 4-aminophenethylamine (9.8 mL, 74.8 mmol) and sodium iodide (4.2 g, 27.93 mmol) were placed in a flask and purged with nitrogen. Methyl sulfoxide (25 mL) was added, and the solution was placed in an oil bath heated at 140°C. The solution was the stirred for 20 min at 140°C. The reaction was allowed to cool to room temperature, then ethyl acetate (300 mL) and H_2O (300 mL) were added. The phases were partitioned, and the organic layer was washed with water (4 x 200mL) and saturated sodium chloride (4 x 200mL). The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum to yield compound **U** (10.5g).

b. Synthesis of compound **W**



Compound **U** (5.18 g, 9.53 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.44 g, 0.48 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.63 g, 0.95 mmol), and sodium t-butoxide (1.83 g, 19.06 mmol) were combined in a flask and purged with nitrogen. 1-Bromo-3-iodobenzene (2.0 mL, 11.44 mmol) was added and the flask was purged again. o-Xylene (50 mL) was added, and the solution was heated at reflux under nitrogen for 2.5 hours, at which time HPLC analysis indicated complete reaction. The o-xylene was removed under vacuum with heating, and dichloromethane (200 mL) was added. Once the residue was dissolved, celite (30 g) was added, and the mixture was filtered and filter cake was washed with dichloromethane until all of the product was collected. The solution was concentrated to dryness under vacuum, redissolved in THF (20 mL), and purged with nitrogen. Tetrabutylammonium fluoride (20 mL, 1.0 M in THF, 20 mmol) was added via syringe, and the solution was stirred for 18 hours at room temperature. The THF was then removed, and the residue was dissolved in DCM, and washed with water (1 x 200 mL) and half-saturated sodium chloride (1 x 200 mL). The organic phase was dried over sodium sulfate, concentrated and chromatographed over silica gel (50g, 0 -10% MeOH in dichloromethane) to yield compound **W** as a yellow solid.

Synthesis of Compounds of Formula (X) - Compounds 66-93:



(X)

Examples 66-69: Synthesis of Compounds 66-69

Using procedures similar to that described in Example 65, except replacing the phenylboronic acid with the appropriate substituted phenylboronic acid, TFA salts of compounds **66-69** were prepared.

Compound **66**: *N*-{2-[4-(3-(2-chlorophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (X) where R^{11} is 2-chlorophenyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.37 (s, 1H), 8.55, (br s, 2H), 8.22, (s, 1H), 8.06 (d, 1H)7.46 (m, 1H), 7.32 (m, 3H), 7.22 (t, 1H), 7.01 (m, 8H), 6.89 (d, 1H), 6.74 (dd, 1H), 6.51 (d, 1H), 6.10 (d, 1H), 3.18 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{31}H_{28}ClN_3O_3$ 526.19; found 526.4.

Compound **67**: *N*-{2-[4-(3-(2-methoxyphenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (X) where R^{11} is 2-methoxyphenyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.40 (s, 1H), 8.60 (br s, 2H), 8.12 (s, 1H), 8.06 (d, 1H), 7.16 (m, 13H), 6.80 (d, 1H), 6.51 (d, 1H) 6.11 (s, 1H) 5.24 (d, 1H), 3.69 (s, 3H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.7.

Compound **68**: Formula (X) where R^{11} is 4-hydroxymethylphenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.39 (s, 1H), 8.60 (br s, 2H), 8.18 (s, 1H), 8.07 (d, 1H), 7.46 (d, 2H), 7.30 (d, 2H), 7.20 (m, 2H), 7.00 (m, 8H), 6.51 (dd, 1H), 6.11 (s, 1H), 5.23 (d, 1H), 4.44 (s, 2H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.4.

Compound **69**: Formula (X) where R^{11} is 4-methoxyphenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.39 (s, 1H) 8.60 (br s, 2H), 8.16 (s, 1H), 8.07 (d, 1H), 7.44 (d, 2H), 6.85-7.20 (m, 12H), 6.51 (dd, 1H), 6.12 (d, 1H), 5.23 (d, 1H), 3.70 (s, 3H), 3.10 (m, 4H), 2.80 (m, 2H) ; *m/z*: [M+H$^+$] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.4.

Example 70: Synthesis of compound 70

Compound **70**: Formula (X) where R^{11} is 4-chlorophenyl

Compound **W** (84.0 mg, 0.143 mmol), 4-chlorophenyl boronic acid (27.2 mg, 0.172 mmol) and [1,1'-bis(diphenylphosphinoferrocene)dichloropalladium (II), complex with dichloromethane ($PdCl_2$(dppf)-DCM) (5.9 mg, 0.007 mmol) were combined in a small pressure tube and purged with N_2. 1,2-Dimethoxyethane (2.0 mL) and 2.0 N

cesium carbonate (150 uL, 0.3 mmol) were added. The tube was sealed, and then placed in an oil bath at 90°C for 4 hours. The solution was then cooled to room temperature and DCM (10 mL) was added. The solution was filtered and concentrated to dryness. To the residue there was added DMF (1.0 mL) and 10% palladium on carbon (10 mg), and the reaction was stirred under one atmosphere of hydrogen for 4 hours. At this time, water:acetonitrile 1:1 and 200 uL TFA was added and the solution was filtered to remove the catalyst. The filtrate was purified by reverse phase HPLC. Fractions containing pure product were combined and lyophilized to give compound **70** as a TFA salt. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.40 (s, 1H), 8.61 (br s, 2H), 8.22 (s, 1H), 8.07 (d, 1H), 7.53 (d, 2H), 7.42 (d, 2H), 7.23 (t, 1H), 7.14 (s, 1H), 6.85-7.10 (m, 8H), 6.51 (d, 1H), 6.12 (s, 1H), 5.24 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{31}H_{28}ClN_3O_3$ 526.19; found 526.4.

Examples 71-72: Synthesis of compounds 71-72

Using procedures similar to that described in Example 70, except replacing the 4-chlorophenylboronic acid with the appropriate substituted boronic acid, TFA salts of compounds **71-72** were prepared.

Compound **71**: Formula (X) where R^{11} is 5-indolyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 11.07 (s, 1H), 10.47 (s, 1H), 10.40 (s, 1H), 8.60 (br s, 2H), 8.15 (s, 1H), 8.11 (d, 1H), 7.65 (s, 1H), 7.15-7.40 (m, 5H), 7.00-7.15 (m, 5H), 6.89 (d, 2H), 6.51 (dd, 1H), 6.39 (s, 1H), 6.11 (s, 1H), 5.24 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{33}H_{30}N_4O_3$ 531.24; found 531.4.

Compound **72**: Formula (X) where R^{11} is 4-pyridyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10 48 (s, 1H) 10.38 (s, 1H), 8.60 (br m, 4H), 8.32 (s, 1H), 8.07 (d, 1H), 7.69 (d, 2H), 7.31 (m, 2H), 7.16 (d, 1H) 7.05 (m, 6H), 6.90 (d, 1H), 6.52 (dd, 1H), 6.11 (s, 1H), 5.24 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{30}H_{28}N_4O_3$ 493.23; found 493.5.

Example 73: Synthesis of compound 73

Compound **73**: Formula (X) where R^{11} is hydrogen: A TFA salt of compound **73** was prepared: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.48 (s, 1H), 10.39 (s, 1H), 8.59 (br s, 2H), 8.07 (dd, 2H), 6.85-7.17 (m, 10H), 6.72 (t, 1H), 6.52 (dd, 1H), 6.11 (d, 1H), 5.22 (d,

1H), 3.10 (m, 4H), 2.80 (m, 2H); m/z: [M+H$^+$] calcd for $C_{25}H_{25}N_3O_3$ 416.20; found 416.3.

Example 74: Synthesis of *N*-{2-[4-(3-(3-cyanophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (74)

Compound **74**: Formula (X) where R^{11} is 3-cyanophenyl

Compound **W** (Example 65, part b) (58.1 mg, 0.100 mmol), 3-cyanophenyl boronic acid (17.6 mg, 0.120 mmol) and [1,1'-bis(diphenylphosphinoferrocene)dichloropalladium (II), complex with dichloromethane ($PdCl_2$(dppf)-DCM) (approximately 6 mg, 0.007 mmol) were combined in a small pressure tube and purged with N_2. 1,2-Dimethoxyethane (2.0 mL) and 2.0 N cesium carbonate (200 uL, 0.4 mmol) were added, the tube was sealed, and then placed in an oil bath at 90°C for 5 hours. The solution was then cooled to room temperature and DCM (10 mL) was added. The solution was dried (Na_2SO_4) for 30 minutes, then filtered, concentrated and dried under vacuum. The residue was dissolved in DCM (2mL) and cooled to 0 °C, then boron trichloride (1.0N in DCM, 1.0mL, 1.0mmol) was added. After 10 minutes the reaction was quenched with methanol (10mL), and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. Fractions containing pure product were combined and lyophilized to give compound **74** as a TFA salt. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.45 (s, 1H), 10.40 (s, 1H), 8.70 (br 2, 2H), 8.34 (m, 1H), 8.09 (d, 1H), 7.97 (s, 1H), 7.85 (dt, 1H), 7.74 (dt, 1H), 7.58 (t, 1H), 7.20-7.30 (m, 2H), 6.95-7.10 (m, 7H), 6.90 (d, 1H), 6.50 (d, 1H), 6.12 (s, 1H), 5.25 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{32}H_{28}N_4O_3$ 517.23; found 517.4.

Examples 75-93: Synthesis of compounds 75-93

Using procedures similar to that described in Example 74, except replacing the 3-cyanophenyl boronic acid with the appropriate substituted boronic acid, TFA salts of compounds **75-93** were prepared.

Compound **75**: Formula (X) where R^{11} is trans-2-phenylvinyl: *m/z*: [M+H$^+$] calcd for $C_{33}H_{31}N_3O_3$ 518.25; found 518.3.

Compound **76**: *N*-{2-[4-(3-(3-pyridyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (X) where R^{11} is 3-pyridyl):

^{1}H NMR (300MHz, DMSO-*d6*) δ 10.38 (br s, 2H), 8.84 (s, 2H), 8.67 (s, 1H), 8.58 (d, 1H), 8.25 (s, 1H), 8.14 (d, 1H), 8.11 (d, 1H), 7.59 (dd, 1H), 7.27 (m, 2H), 7.05 (m, 7H), 6.90 (d, 1H), 6.50 (d, 1H), 5.28 (d, 1H), 3.10 (m, 4H), 2.83 (m, 2H). m/z: [M+H$^+$] calcd for $C_{30}H_{28}N_4O_3$ 493.23; found 493.5.

Compound **77**: Formula (X) where R^{11} is 4-cyanophenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ10.45 (br s, 1H), 10.40 (s, 1H), 8.62 (br, s, 2H), 8.27 (s, 1H), 8.07 (d, 1H), 7.84 (d, 2H), 7.72 (d, 2H), 7.27 (m, 2H), 7.18 (m, 7H), 6.91 (d, 1H), 6.52 (d, 1H), 6.12 (s, 1H), 5.24 (m, 1H), 3.12 (m, 4H), 2.81 (m, 2H). *m/z*: [M+H$^+$] calcd for $C_{32}H_{28}N_4O_3$ 516.60; found 517.4.

Compound **78**: Formula (X) where R^{11} is 3,5-dimethylisoxazole-4-yl: *m/z*: [M+H$^+$] calcd for $C_{30}H_{30}N_4O_4$ 511.24; found 511.5.

Compound **79**: Formula (X) where R^{11} is 2-furanyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 11.15 (s, 1H), 10.47 (s, 1H), 10.41 (s, 1H), 8.64 (br s, 1H), 8.10 (t, 2H), 7.08 (m, 9H), 6.77 (s, 1H), 6.74 (s, 1H), 6.52 (d, 1H), 6.30 (s, 1H), 6.12 (s, 1H), 6.02 (q, 1H), 5.25 (d, 1H), 3.10 (m, 4H), 2.85 (m, 2H). *m/z* [M+H$^+$] calcd for $C_{29}H_{27}N_3O_4$ 482.21; found 481.4.

Compound **80**: Formula (X) where R^{11} is thiophene-2-yl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.38 (s, 1H), 8.62 (br s, 2H), 8.22 (s, 1H), 8.07 (d, 1H), 7.44 (d, 1H), 7.33 (d, 1H), 7.35 (m, 2H), 7.06 (m, 7H), 6.90 (d, 2H), 6.50 (d, 1H), 6.10 (d, 1H), 5.23 (m, 1H), 3.10 (m, 4H), 2.85 (m, 2H). *m/z* [M+H$^+$] calcd for $C_{29}H_{27}N_3O_3S$ 498.19; found 498.5.

Compound **81**: Formula (X) where R^{11} is 3-nitrophenyl: *m/z*: [M+H$^+$] calcd for $C_{31}H_{28}N_4O_5$ 537.22; found 537.3.

Compound **82**: Formula (X) where R^{11} is 4-formylphenyl: *m/z*: [M+H$^+$] calcd for $C_{32}H_{29}N_3O_4$ 520.23; found 520.5.

Compound **83**: Formula (X) where R^{11} is 2-pyrrolyl: Using a procedure similar to that described in Example 74, except replacing the 3-cyanophenylboronic acid with 1-(*tert*-butoxycarbonyl)pyrrole-2-boronic acid, a TFA salt of compound **83** was prepared. Deprotection of the Boc group occurred under reaction conditions. ^{1}H NMR (300MHz, DMSO-*d6*) δ 11.13 (s, 1H), 10.46 (s, 1H), 10.37 (s, 1H), 8.58 (br s, 2H), 8.08 (s, 1H), 8.05 (s, 1H), 7.05 (m, 9H), 6.75 (s, 1H), 6.73 (s, 1H), 6.51 (d, 1H), 6.23 (s, 1H), 6.08 (s,

1H), 6.01 (s, 1H), 5.22 (m, 1H), 3.12 (m, 4H), 2.80 (m, 2H). *m/z*: [M+H$^+$] calcd for $C_{29}H_{28}N_4O_3$ 481.23; found 481.3.

Compound **84**: Formula (X) where R^{11} is 4-carboxyphenyl: *m/z*: [M+H$^+$] calcd for $C_{32}H_{29}N_3O_5$ 536.22; found 536.3.

Compound **85**: Formula (X) where R^{11} is 4-methylsulfonylphenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.45 (s, 1H), 10.38 (s, 1H), 8.58 (br s, 1H), 8.27 (s, 1H), 8.05 (d, 1H), 7.90 (d, 2H), 7.77 (d, 2H), 7.26 (m, 2H), 7.04 (m, 7H), 6.88 (d, 1H), 6.50 (d, 1H), 6.11 (s, 1H), 5.22 (d, 1H), 3.16 (s, 3H), 3.11 (m, 4H), 2.80 (m, 2H) . *m/z*: [M+H$^+$] calcd for $C_{32}H_{31}N_3O_5S$ 570.21; found 570.3.

Compound **86**: Formula (X) where R^{11} is 4-hydroxyphenyl: Using a procedure similar to that described in Example 74, except replacing the 3-cyanophenylboronic acid with 4-benzyloxyphenylboronic acid, a TFA salt of compound **86** was prepared. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.40 (s, 1H), 9.47 (s, 1H), 8.71 (br s, 2H), 8.12 (m, 2H), 7.32 (d, 2H), 7.02 (m, 9H), 6.75 (d, 2H), 6.51 (d, 1H), 6.10 (s, 1H), 5.25 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H). *m/z*: [M+H$^+$] calcd for $C_{31}H_{29}N_3O_4$ 508.23; found 508.3.

Compound **87:** *N*-{2-[4-(3-(4-aminomethylphenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (X) where R^{11} is 4-(aminomethyl)phenyl): *m/z*: [M+H$^+$] calcd for $C_{32}H_{32}N_4O_3$ 521.26; found 521.3.

Compound **88**: Formula (X) where R^{11} is 4-ethoxyphenyl: *m/z*: [M+H$^+$] calcd for $C_{33}H_{33}N_3O_4$ 536.26; found 536.3.

Compound **89**: Formula (X) where R^{11} is thiophene-3-yl: *m/z*: [M+H$^+$] calcd for $C_{29}H_{27}N_3O_3S$ 498.19; found 498.3.

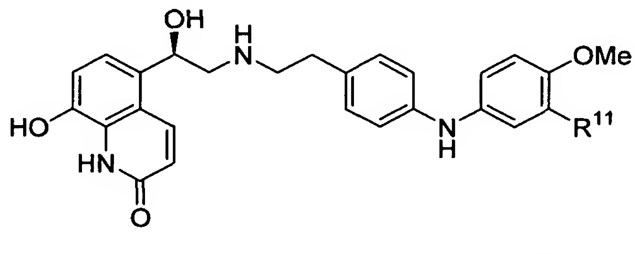
Compound **90**: Formula (X) where R^{11} is 2-indolyl: *m/z*: [M+H$^+$] calcd for $C_{33}H_{30}N_4O_3$ 531.24; found 531.3.

Compound **91:** *N*-{2-[4-(3-(3-chlorophenyl)phenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (X) where R^{11} is 3-chlorophenyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.45 (s, 1H), 10.38 (s, 1H), 8.58 (br s, 2H), 8.20 (s, 1H), 8.06 (d, 1H), 7.21 (m, 14H), 6.51 (d, 1H), 6.10 (s, 1H), 5.23 (d, 1H), 3.10 (m, 4H), 2.80 (m, 2H). [M+H] calcd for $C_{31}H_{28}ClN_3O_3$ 526.03; found 526.3.

Compound **92**: Formula (X) where R^{11} is 3-methoxyphenyl: *m/z*: [M+H] calcd for $C_{32}H_{31}N_3O_4$ 522.24; found 522.0.

Compound **93**: Formula (X) where R^{11} is 3-fluorophenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.42 (s, 1H), 10.39 (s, 1H), 8.60 (br s, 2H), 8.20 (s, 1H), 8.15 (d, 1H), 7.2 (m, 14H), 6.51 (d, 1H), 6.11 (s, 1H), 5.23 (d, 1H), 3.10 (m, 4H), 2.81 (m, 2H). *m/z*: [M+H$^+$] calcd for $C_{31}H_{28}FN_3O_3$ 509.58; found 510.3.

Synthesis of Compounds of Formula (XI) - Compounds 94-101



(XI)

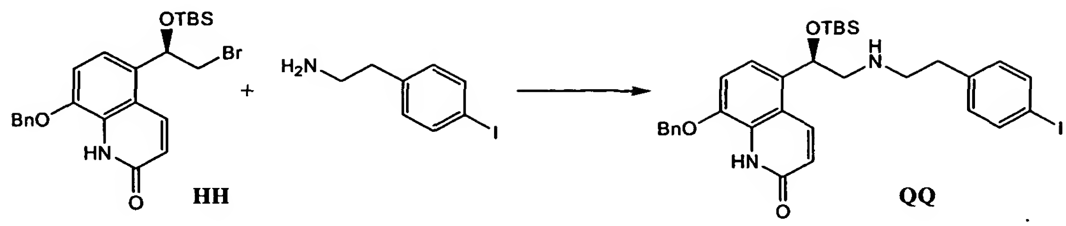
Example 94: Synthesis of *N*-{2-[4-(3-(3-pyridyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (94)

Compound **94:** Formula (XI) where R^{11} is 3-pyridyl

a. Synthesis of 4-iodophenethylamine

4-Iodophenylacetonitrile (4.80 g, 19.7 mmol) was dissolved in tetrahydrofuran (25 mL) under nitrogen, and 1.0 M borane in tetrahydrofuran (29.6 mL, 29.6 mmol) was added via syringe. The reaction was heated at reflux for 1 hour, then cooled in ice and the excess borane was quenched by the addition of methanol (100 mL). When hydrogen evolution ceased, the solvents were removed under reduced pressure. The residue was dissolved in tetrahydrofuran (25 mL) and 4N HCl in dioxane (6.0 mL, 24 mmol) was added, followed by ether (75 mL). The hydrochloride salt of 4-iodophenethylamine was collected on a Buchner funnel, washed with ether (2x50 mL) and dried under reduced pressure. To generate the free base, the solid was partitioned between dichloromethane (200 mL) and 1N NaOH (100 mL). The aqueous layer was extracted with dichloromethane (2x100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 4-iodophenethylamine (4.52 g) as a colorless oil.

b. Synthesis of compound **QQ**

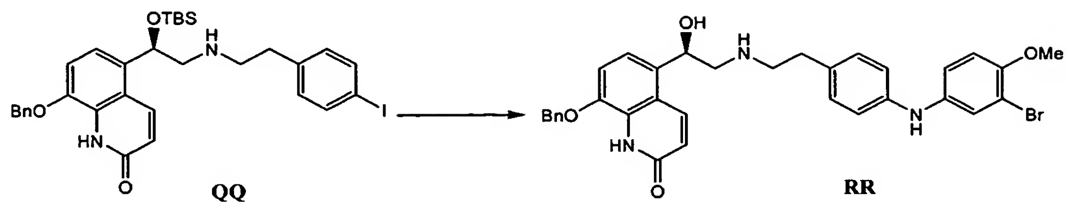


To a solution of 4-iodophenethylamine (4.5 g, 22 mmol) in methyl sulfoxide (13 mL) under nitrogen was added compound **HH** (from Example 61B part f) (7.3 g, 15 mmol), sodium bicarbonate (3.7 g, 44 mmol) and sodium iodide (3.3 g, 22 mmol). The mixture was heated at 140°C in an oil bath for 25 minutes. After cooling to room temperature, water (100 mL) was added and the resulting mixture was extracted with ethyl acetate (2x150 mL). The combined extracts were washed with 1N HCl (2x50 mL), water (50 mL) 10% sodium thiosulfate (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The solution was dried (Na_2SO_4) and concentrated. The crude product was purified in two lots by flash chromatography on silica gel (75 g) eluting with 0-5% methanol in dichloromethane containing 0.5% triethylamine. Compound **QQ** (6.1 g) was isolated as a dark yellow oil.

c. Synthesis of 4-amino-2-bromoanisole

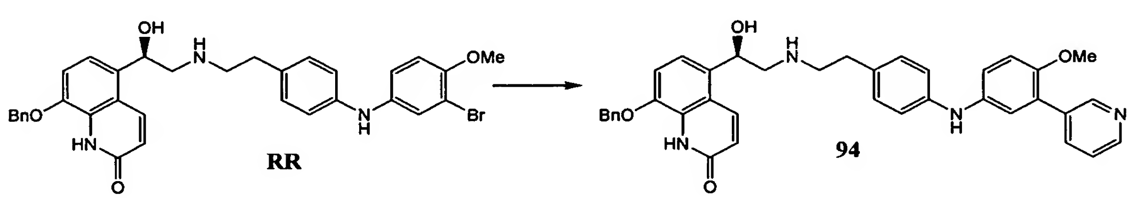
To a mixture of 2-bromo-4-nitroanisole (5.0 g, 21.5 mmol, Lancaster), ethanol (25 mL) and water (25 mL), was added powdered iron (4.8 g, 86 mmol) and 12 N HCl (0.5 mL). The solution was heated at reflux for 20 minutes. 1N NaOH (10 mL) was added and the reaction mixture was filtered through a pad of celite while still hot, and then rinsed with ethanol (2x50 mL). The ethanol was removed under reduced pressure and the residue extracted with dichloromethane (2x100 mL). The organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on silica gel (75 g) eluting with dichloromethane, to give 4-amino-2-bromoanisole as a light tan solid.

d. Synthesis of compound **RR**



A flask containing compound **QQ** (0.966 g, 1.48 mmol), 4-amino-2-bromoanisole (0.35 g, 1.78 mmol), tris(dibenzylidineacetone)dipalladium(0) (0.068 g, 0.074 mmol), BINAP (0.092 g, 0.148 mmol), and sodium *tert*-butoxide (0.569 g, 5.92 mmol) was flushed with nitrogen, and then anhydrous *o*-xylene (30 mL) was added. The mixture was heated at 115°C in an oil bath for two hours. At this time, the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The brownish residue was redissolved in dichloromethane and filtered through a bed of celite. The filtrate was concentrated to dryness under reduced pressure, dissolved in THF (20 mL) and purged with nitrogen. Tetrabutylammonium fluoride (1.0 N in THF, 4.5 mL, 4.5 mmol) was added and the solution was stirred for 18 hours at room temperature. The solvent was removed under reduced pressure, and the residue partitioned between water and DCM. The organic layer was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1-10% MeOH in DCM) to give compound **RR**.

e. Synthesis of compound **94**



Into a nitrogen purged test tube with a screw cap was placed compound **RR** (73 mg, 0.12 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) dichloromethane complex (10 mg) and 3-pyridylboronic acid (18 mg, 0.14 mmol). Dimethoxyethane (2.5 mL) was added, followed by 2.0 N cesium carbonate (0.20 mL,

0.40 mmol). The mixture was heated at 90°C for 4 hours. The solution was then cooled to room temperature and DCM (20 mL) was added. The solution was dried (Na_2SO_4) for 30 minutes, then filtered, concentrated and dried under vacuum. The residue was dissolved in DCM (2 mL) and cooled to 0 °C, and then boron trichloride (1.0N in DCM, 1.0 mL, 1.0 mmol) was added. After 10 minutes the reaction was quenched with methanol (10 mL), and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. Fractions containing pure product were combined and lyophilized to give a TFA salt of *N*-{2-[4-(3-(3-pyridyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine **(94)**. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.; m/z: [M+H$^+$] calcd for $C_{31}H_{30}N_4O_4$ 523.24; found 523.3.

A sample of the TFA salt (25 mg) was dissolved in acetonitrile (0.5 mL) and water (0.5 mL), followed by 1N HCl (0.10 mL, 0.10 mmol). The solution was lyophylized to a powder which was redissolved in acetonitrile (0.5 mL) and water (0.5 mL). 1N HCl was then added (0.10mL, 0.10mmol). Lyophylization gave a hydrochloride salt of compound **94** as an off white powder. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.49 (br s, 1H), 9.44 (br s, 1H), 8.97 (d, 1H), 8.78 (d, 1H), 8.77 (br s, 1H), 8.61 (dt, 1H), 8.20 (d, 1H), 8.01 (dd, 1H), 6.90-7.15 (m, 8H), 6.47 (d, 1H),5.39 (d, 1H), 3.70 (s, 3H), 3.02 (m, 4H), 2.82 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{31}H_{30}N_4O_4$ 523.24; found 523.6.

Example 95: Synthesis of *N*-{2-[4-(3-(3-cyanophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (95)

Compound **95:** Formula (XI) where R^{11} is 3-cyanophenyl.

Into a nitrogen purged test tube with a screw cap was placed compound **RR** (from Example 94, part d) (100 mg, 0.163 mmol), [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) dichloromethane complex (10 mg) and 3-cyanophenylboronic acid (35 mg, 0.20 mmol). Dimethoxyethane (3 mL) was added, followed by 2.0 N cesium carbonate (0.30 mL, 0.60 mmol). The mixture was heated at 90°C for 4 hours. The solution was then cooled to room temperature and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4), concentrated and dried under reduced pressure. The residue was dissolved in DCM (5 mL) and cooled to 0 °C, and then boron trichloride (1.0 N in DCM, 2.0mL, 2.0 mmol) was added. After 10 minutes the reaction was quenched with methanol (20 mL), and concentrated under

reduced pressure. The residue was purified by reverse phase HPLC. Fractions containing pure product were combined and lyophilized to give a TFA salt of compound **95**. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.38 (s, 1H), 8.57 (br s, 2H) 8.05 (d, 1H), 7.89 (m, 1H), 7.82 (m, 1H), 7.70 (m, 2H), 7.53 (t, 2H), 7.07 (d, 1H), 6.95-7.00 (m, 4H), 6.85-6.92 (m, 3H), 6.50 (dd, 1H), 6.09 (d, 1H), 5.22 (d, 1H), 3.65 (s, 3H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{33}H_{30}N_4O_4$ 547.24; found 547.5.

Examples 96-102: Synthesis of Compounds 96-102

Using procedures similar to that described in Example 95, except replacing the 3-cyanophenylboronic acid with the appropriate substituted phenylboronic acid, TFA salts of compounds **96-102** were prepared.

Compound **96**: *N*-{2-[4-(3-(4-aminomethylphenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (XI) where R^{11} is 4-(aminomethyl)phenyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.40 (s, 1H), 8.58 (br s, 2H), 8.07 (m, 4H), 7.87 (s, 1H), 7.40 (dd, 4H), 7.07 (d, 1H), 6.84-7.05 (m, 8H), 6.50 (dd, 1H), 6.11 (d, 1H), 5.23 (d, 1H), 3.98 (m, 2H), 3.62 (s, 3H), 3.05 (m, 2H), 2.95 (m, 2H), 2.75 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{33}H_{34}N_4O_4$ 551.27; found 551.5.

Compound **97** *N*-{2-[4-(3-(4-pyridyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (XI) where R^{11} is 4-pyridyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.42 (s, 1H), 8.65 (d, 2H), 8.62 (br s, 1H), 8.06 (d, 2H), 7.97 (br s, 1H), 7.73 (d, 2H) 6.95-7.10 (m, 7H), 6.90 (dd, 2H), 6.12 (br s, 1H), 5.23 (d, 1H), 3.69 (s, 3H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{31}H_{30}N_4O_4$ 523.24; found 523.6.

Compound **98**: Formula (XI) where R^{11} is 4-formylphenyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.39 (s, 1H), 9.95 (s, 1H), 8.57 (br s, 2H), 8.05 (d, 1H), 7.91 (br s, 1H), 7.85 (d, 2H), 7.61 (d, 2H), 6.95-7.10 (m, 7H), 6.89 (dd, 2H), 6.50 (dd, 1H), 6.10 (s, 1H), 5.22 (d, 1H), 3.65 (s, 3H), 3.05 (m, 4H), 2.75 (m, 2H) ; *m/z*: [M+H$^+$] calcd for $C_{33}H_{31}N_3O_5$ 550.24; found 550.6.

Compound **99**: Formula (XI) where R^{11} is 4-methylsulfonyl: ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.38 (s, 1H), 8.55 (br s, 2H), 8.05 (d, 1H), 7.91 (s, 1H), 7.86 (d, 2H), 6.74 (d, 2H), 6.93-7.10 (m, 6H), 6.85-6.92 (m, 3H), 6.51 (dd, 1H), 6.09 (d, 1H),

5.22 (d, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 3.05 (m, 4H), 2.75 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{33}H_{33}N_3O_6S$ 600.22; found 600.5.

Compound **100:** *N*-{2-[4-(3-(4-hydroxyphenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (XI) where R^{11} is 4-hydroxyphenyl): Using a procedure similar to that described in Example 95, except replacing the 3-cyanophenylboronic acid with 4-benzyloxyphenylboronic acid, a TFA salt of compound **100** was prepared. ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.38 (s, 1H), 9.34 (s, 1H), 8.57 (br s, 2H), 8.06 (d, 1H), 7.80 (s, 1H), 7.18 (d, 2H), 7.07 (d, 1H), 6.97 (d, 2H), 6.80-6.90 (m, 6H), 6.69 (d, 2H), 6.51 (dd, 1H), 6.09 (s, 1H), 5.23 (d, 1H), 3.60 (s, 3H), 3.05 (m, 4H), 2.78 (m, 2H); *m/z*: [M+H] calcd for $C_{32}H_{31}N_3O_5$ 538.24; found 538.5.

Compound **101:** *N*-{2-[4-(3-(thiophen-3-yl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (XI) where R^{11} is thiophen-3-yl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.47 (s, 1H), 10.38 (s, 1H), 8.57 (br s, 2H), 8.06 (d, 1H), 7.83 (s, 1H), 6.74 (dd, 1H), 7.48 (dd, 1H), 7.31 (dd, 1H), 7.13 (s, 1H), 7.06 (d, 1H), 6.80-7.00 (m, 7H), 6.51 (dd, 1H), 6.01 (s, 1H), 5.23 (d, 1H), 3.70 (s, 3H), 3.07 (m, 4H), 2.77 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{30}H_{29}N_3O_4S$ 528.20; found 528.3.

Compound **102:** *N*-{2-[4-(3-(3-chlorophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (Formula (XI) where R^{11} is 3-chlorophenyl): ^{1}H NMR (300MHz, DMSO-*d6*) δ 10.46 (s, 1H), 10.38 (s, 1H), 8.76 (br s, 1H), 8.62 (br s, 1H), 8.10 (s, 1H), 7.88 (br s, 1H), 7.15-7.23 (m, 5H), 6.85-7.10 (m, 11H), 6.50 (d, 1H), 6.09 (br s, 1H), 5.27 (d, 1H), 3.65 (s, 3H), 3.10 (m, 4H), 2.80 (m, 2H); *m/z*: [M+H$^+$] calcd for $C_{32}H_{30}ClN_3O_4$ 556.20; found 556.2.

Example 103: Synthesis of *N*-{2-[4-(3-(3-cyanophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (95)

Using procedures similar to those described in Example 61C and the deprotection step of Example 61B, except replacing the 4-methoxy-3-phenylaniline hydrochloride with 3-(3-cyanophenyl)-4-methoxyaniline in Example 61C, part d, compound **95** was prepared.

The intermediate compound 3-(3-cyanophenyl)-4-methoxyaniline was prepared as follows:

a. Synthesis of 2-(3-cyanophenyl)-4-nitroanisole

[1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane(1:1) (1.43 g) was added to a stirred mixture of 3-cyanophenylboronic acid (10.0 g, 61.8 mmol) and 2-bromo-4-nitroanisole (14.35 g, 62 mmol) in 2.0N cesium carbonate (92.7 mL, 185.4 mmol) and ethylene glycol dimethylether (200 mL). The flask was purged with nitrogen and heated at 90°C (oil bath) for 4 hours. The mixture was allowed to cool to room temperature overnight, during which time the product precipitated from solution. The solid was collected on a Buchner funnel, washed with water and dried under reduced pressure to give 2-(3-cyanophenyl)-4-nitroanisole (15.7 g).

b. Synthesis of 3-(3-cyanophenyl)-4-methoxyaniline

Zinc dust (20.26g, 310mmol) was added in portions over five minutes to a solution of 2-(3-cyanophenyl)-4-nitroanisole (15.7 g , 62 mmol) and ammonium formate (19.48 g, 310 mmol) in methanol (500 mL) and tetrahydofuran (500 mL). The reaction was complete after stirring for one hour at room temperature. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified using flash chromatoghraphy on silica gel eluting with 5% methanol in dichloromethane to give 3-(3-cyanophenyl)-4-methoxyaniline (10 g, 44 mmol) as a yellow oil.

Example 104: Synthesis of *N*-{2-[4-(3-(4-aminomethylphenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (96)

Using procedures similar to those described in Example 61C and the deprotection step of Example 61B, except replacing the 4-methoxy-3-phenylaniline hydrochloride with 3-(4-aminomethylphenyl)-4-methoxyaniline in Example 61C, part d, compound **96** was prepared.

The intermediate compound 3-(4-aminomethylphenyl)-4-methoxyaniline was prepared as follows:

a. Synthesis of 2-(4-aminomethylphenyl)-4-nitroanisole

A mixture of 2-bromo-4-nitroanisole (5.80 g, 25.0 mmol) and 4-(aminomethyl)phenylboronic acid hydrochloride (4.96 g, 26.6 mmol) was slurried in 1-propanol (50 mL) under nitrogen. Triphenylphosphine (315 mg, 1.20 mmol) and palladium (II) acetate (90 mg, 0.40 mmol) were added, followed by 2.0N sodium

carabonate(33mL, 66mmol). The mixture was heated at 95°C (oil bath) under nitrogen for 3 hours, at which time the reaction was judged to be complete by TLC. Water (25 mL) was added and the mixture was stirred open to air for 2 hours at room temperature. The mixture was extracted with ethyl acetate (100 mL, 2x50 mL) and the combined extracts were washed with sodium bicarbonate (25 mL) and brine (25 mL). The solution was dried with sodium sulfate, and concentrated to an oil which was purified by flash chromatography on silica gel (100 g) eluting with 0-4% methanol/0,5% triethylamine/dichloromethane. Pure fractions were combined and concentrated to give 2-(4-aminomethylphenyl)-4-nitroanisole (4.6 g) as a yellow solid.

b. Synthesis of 3-(4-aminomethylphenyl)-4-methoxyaniline

A solution of 2-(4-aminomethylphenyl)-4-nitroanisole (4.50g) in methanol (200 mL) was treated with 10% palladium on carbon (200mg). The reaction mixture was stirred under one atmosphere of hydrogen for 2.5 hours. The reaction mixture filtered through Celite, and the filter cake was washed with methanol (3x25mL). The filtrate was concentrated to dryness and the residue was purified by flash chromatography on silica gel (80 g) eluting with 0-6% methanol/0.5% triethylamine/dichloromethane. Pure fractions were combined and concentrated to give 3-(4-aminomethylphenyl)-4-methoxyaniline as an off white powder.

Example 105: Synthesis of *N*-{2-[4-(3-(3-chlorophenyl)-4-methoxyphenyl)aminophenyl]ethyl}-(*R*)-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine (102)

Using procedures similar to those described in Example 61C and the deprotection step of Example 61B, except replacing the 4-methoxy-3-phenylaniline hydrochloride with 3-(3-chlorophenyl)-4-methoxyaniline in Example 61C, part d, compound **102** was prepared.

The intermediate compound 3-(3-chlorophenyl)-4-methoxyaniline was prepared as follows:

a. Synthesis of 2-(3-chlorophenyl)-4-nitroanisole

To a flask containing a bi-phasic mixture of 2-bromo-4-nitroanisole (15.0 g, 64.6 mmol) and 3-chlorophenylboronic acid (12.1 g, 77.6 mmol) in ethylene glycol dimethyl ether (187.5 mL) and 2.0 N aqueous cesium carbonate (97 mL) was added 1-1'-

bis(diphenylphosphino)ferrocene)dichloro palladium (II), complex with dichloromethane (1:1) (1.5 g). The mixture was heated at reflux for 4 hours under a nitrogen atmosphere. The crude reaction mixture was partitioned between ethyl acetate (350 mL) and brine (250 mL) and then filtered through a Buchner funnel. Layers were separated and the organic layer was washed with brine (250 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to a dark oil. The crude residue was purified by flash chromatography on silica gel using dichloromethane as the eluent to afford 2-(3-chlorophenyl)-4-nitroanisole as a yellow solid (13.9 g, 59.4 mmol).

b. Synthesis of 3-(3-chlorophenyl)-4-methoxyaniline

To a mixture of 2-(3-chlorophenyl)-4-nitroanisole (0.5 g, 1.9 mmol)in tetrahydrofuran (5 mL) and methanol (5 mL) was added platinum (IV) oxide (1 mg). The reaction was stirred at room temperature under one atmosphere of hydrogen for 4.5 hours. The slurry was filtered through Celite and concentrated under reduced pressure to afford 3-(3-chlorophenyl)-4-methoxyaniline as a light yellow oil (405 mg, 1.7 mmol).

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. Additionally, all publications, patents, and patent documents cited hereinabove are incorporated by reference herein in full, as though individually incorporated by reference.